GEORGIA INSTITUTE OF TECHNOLOGY — OFFICE OF CONTRACT ADMINISTRATION

PROJECT ADMINISTRATION DATA SHEET

[x] ORIGINAL [ ] REVISION NO. _____

Project No. G-33-601 GTRI/GIT DATE 5 /17 /84

Project Director: Dr. Eugene C. Ashby School/DBS Chemistry

Sponsor: National Science Foundation

Type Agreement: Grant No. CHE-8403024

Award Period: From 6/1/84 To ~~11/30/85~~ * (Performance) ~~5/31/89~~ 5/31/89 (Reports)

Sponsor Amount:	This Change	Total to Date
Estimated: $		$ 103,000
Funded: $		$ 103,000

Cost Sharing Amount: $ 5,422 Cost Sharing No: G-33-334

Title: "Single Electron Transfer.A Major Reaction Pathway in Organic Chemistry"

ADMINISTRATIVE DATA OCA Contact Lynn Boyd x4820

1) Sponsor Technical Contact:

J. Eric Nordlander
Program Office for Chemical Organics
National Science Foundation
Washington, DC 20550

(202) 357-7956

2) Sponsor Admin/Contractual Matters:

Dionie Henry
Grants Official
National Science Foundation
Washington, DC 20550

(202) 357-9651

Defense Priority Rating: _____ Military Security Classification: _____

(or) Company/Industrial Proprietary: _____

RESTRICTIONS

See Attached NSF Supplemental Information Sheet for Additional Requirements.

Travel: Foreign travel must have prior approval – Contact OCA in each case. Domestic travel requires sponsor approval where total will exceed greater of $500 or 125% of approved proposal budget category.

Equipment: Title vests with GIT.

COMMENTS:

* The usual 6 month unfunded flexibility period is included.

This is the first year of 3 year continuing grant.

Sponsor I.D. #02.107.000.84.040

COPIES TO:

Project Director
Research Administrative Network
Research Property Management
Accounting
Procurement/EES Supply Services
Research Security Services
Reports Coordinator (OCA)
Research Communications (2)
GTRI
Library
Project File
Other Newton

FORM OCA 4:383

GEORGIA INSTITUTE OF TECHNOLOGY
OFFICE OF CONTRACT ADMINISTRATION

NOTICE OF PROJECT CLOSEOUT

SR522

Closeout Notice Date 07/20/90

Project No. G-33-601 Center No. R5753-0A0

Project Director ASHBY E C School/Lab CHEMISTRY

Sponsor NATL SCIENCE FOUNDATION/GENERAL

Contract/Grant No. CHE-8403024 Contract Entity GTRC

Prime Contract No.

Title SINGLE ELECTRON TRANSFER. A MAJOR REACTION PATHWAY IN ORGANIC CHEMISTRY

Effective Completion Date 900531 (Performance) 900831 (Reports)

Closeout Actions Required:	Y/N	Date Submitted
Final Invoice or Copy of Final Invoice	N	
Final Report of Inventions and/or Subcontracts	N	
Government Property Inventory & Related Certificate	N	
Classified Material Certificate	N	
Release and Assignment	N	
Other	N	

Comments

Subproject Under Main Project No.

Continues Project No.

Distribution Required:

Project Director	Y
Administrative Network Representative	Y
GTRI Accounting/Grants and Contracts	Y
Procurement/Supply Services	Y
Research Property Managment	Y
Research Security Services	N
Reports Coordinator (OCA)	Y
GTRC	Y
Project File	Y
Other	N
	N

G-33-601

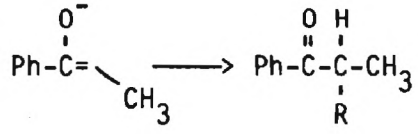
Summary of Progress (the past three years, June 1, 1984-March 31, 1987)

Since the last proposal submitted three and one half years ago, the following reactions have been studied in detail, the work completed and results published. The reactions fall into two major categories: I, the reactions of alkyl halides with nucleophiles and II, the reactions of aromatic ketones with nucleophiles.

I. $RX + Y^- \longrightarrow RY + X^-$

(1) $RX + LiAlH_4 \longrightarrow RH$ — J. Org. Chem. **1984**, 49, 3545; J. Org. Chem. **1984**, 49, 4505; J. Org. Chem. **1986**, 51, 3598

(2) $RX + Me_3Sn^- \longrightarrow RSnMe_3$ — Organometallics **1984**, 3, 1718; Organometallics **1984**, 4, 1493

(3)  — J. Org. Chem. **1985**, 50, 3274

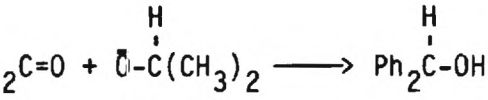
(4) $RX + SR'^- \longrightarrow RSR'$ — J. Org. Chem. **1985**, 50, 5184

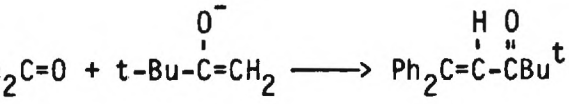
(5) $RX + R'Li \longrightarrow RLi + R'X$ — J. Org. Chem. **1987**, 52, 0000

(6) $RX + LiCuR'_2 \longrightarrow R - R'$ — J. Org. Chem. **1987**, submitted

(7) New Radical Probes — Tetrahedron Lett. **1984**, 25, 4333

II. $Ph_2C{=}O + Y^- \longrightarrow$

(1)  — J. Org. Chem. **1986**, 51, 472

(2)  — J. Org. Chem. **1986**, 51, 3593

(3) $PhCH{=}O + OH^- \longrightarrow PhCO^- + PhCH_2OH$ — J. Org. Chem. **1987**, 52, submitted

(4) $Ph_2C{=}O + Ph_3P{=}CH_2 \longrightarrow Ph_2C{=}H_2$ — J. Org. Chem. **1987**, 52, submitted

In addition to the above, four Communications were published:

Tetrahedron Lett. **1984**, 25, 7

1984, 25, 5107

1985, 26, 4691

1986, 27, 465

Research to be Conducted

The Mechanism of Nucleophilic Aliphatic Substitution

Nucleophilic aliphatic substitution involving the reactions of nucleophiles with alkyl halides is one of the most fundamental reactions in organic chemistry. It is becoming increasingly clear that some reactions heretofore considered to be classic S_N2 processes, because of their exhibited characteristic of inversion of the reaction center, are actually electron transfer processes involving radical intermediates. We believe that reactions considered to be classic S_N2 reactions that do not proceed with 100% inversion of configuration give evidence of either an exclusive alternate pathway or a competing one. The suggestion is that the alternate pathway is a one electron transfer process involving transfer of an electron from the nucleophile to the lowest lying anti-bonding orbital of the substrate. When a substrate is difficult to reduce (large negative reduction potential), a S_N2 pathway predominates; however, when the substrate is easy to reduce (smaller negative reduction potential), one electron transfer is favored.

In the past three years we have published 16 papers concerned with the reactions of alkyl halides and/or ketones with RLi, $LiAlH_4$, cuprates, enolates, Me_3Sn^-, and thiolates and in each case have reported evidence for single electron transfer (SET). In addition, secondary optically active alkyl halides have been employed in some of the reactions mentioned above in order to compare the degree of racemization in a particular reaction with the degree of cyclization of a structurally similar radical probe in the same reaction. For example, we have reported that the reaction

of (+)-2-iodooctane and 6-iodo-1-heptene with $LiAlH_4$ and Me_3Sn gave evidence of a radical intermediate, yet the observation of inversion of configuration.

Formation of cyclized substitution product involving 6-iodo-1-heptene has been suggested as evidence for a radical intermediate and the absence of cyclized product has been erroneously interpreted as evidence for the absence of a radical intermediate. However, since cyclized substitution product results only after diffusion of the radical from the solvent cage, it is not surprising that rapid geminate coupling of radicals inside the solvent cage gives no evidence of a radical intermediate. On the other hand, a chiral center should lose its stereochemical integrity inside the solvent cage at a rate at least competitive with that of geminate coupling. The extent of loss of stereochemical integrity should then be a measure of the extent of radical formation in the solvent cage. Thus, a method exists for determining the intermediate formation of radicals in a reaction even when the radicals are not detectable by cyclization, trapping or direct observation by esr. Using chirality as a proble, we have found six nucleophiles that react with optically active 2-substituted octanes resulting in a loss of optical activity of the product as the leaving group proceeds from tosylate, to chloride, to bromide, to iodide (some of the data reported in the table).

Although inversion of configuration has normally been considered adequate indication of a S_N2 processes, it is now clear that inversion of configuration can also result from a SET process due to rapid geminate coupling of incipient radicals inside the solvent cage. Since RX compounds are more easily reduced in the order X = I>Br>CI>OTs, reactions of tosylates are more likely to react by a S_N2 pathway whereas iodides are more likely to react by SET.

There is evidence that a carbonium ion is not formed in any of the reactions with the nucleophiles studied; however, the intermediacy of carbonium ions in these

Table. Reactions of 2-Halooctanes with Nucleophiles in DMF at Room Temperature.

Nuc	R*X	Product % opt. Purity	% Inversion
LiSPh	OTs	100.0	100.0
"	Cl	99.1	99.5
"	Br	99.3	99.6
"	I	77.2	88.6
$LiSPr^i$	OTs	100.0	100.0
"	Cl	99.6	99.8
"	Br	71.5	85.7
"	I	70.1	85.1
LiCN	OTs	100.0	100.0
"	Br	67.2	83.6
"	I	65.8	82.9
$LiPPh_2$	OTs	100.0	100.0
"	Cl	100.0	100.0
"	Br	87.6	93.8
"	I	88.1	94.0

reactions is a crucial matter and this point needs to be addressed diligently. There are several important things to do: (1) study the reaction of optically active halides with more nucleophiles, (2) study the reaction with more leaving groups, (3) carry out a more extensive solvent study and (4) use probes that will result in carbonium ion rearrangement as well as loss of stereochemical integrity at the chiral center. The results of such studies should support the notion that has been proposed and that is, that many important reactions in organic chemistry heretofore believed to be polar S_N2 processes by virtue of the observation of inversion of configuration of the reaction center, can also be radical reactions that proceed with predominant inversion of configuration. In addition to this project we are also studying the mechanism of 1,2 and 1,4-addition of organometallic compounds to enones and the mechanism of reaction of alkyl halides with magnesium, lithium and zinc.

G-33-601

Summary of Progress December 1, 1987 - November 30, 1988

Since the last report submitted to NSF August 12, 1987, the following papers have been published on the NSF program:

1. Ashby, E.C.; Pham, Tung N. J. Org. Chem. 1987, 52, 1291. "Single Electron Transfer in Metal-Halogen Exchange. The Reaction of Organolithium Compounds with Alkyl Halides."

2. Ashby, E.C.; Coleman, David; Gamasa, Maria J. Org. Chem. 1987, 52, 4079. "Single Electron Transfer in the Cannizzaro Reaction."

3. Ashby, E.C.; Coleman, David J. Org. Chem. 1987, 52, 4554. "Evidence for Single Electron Transfer in the Reactions of Lithium Dimethylcuprate with Alkyl Halides."

4. Ashby, E.C.; Pham, Tung N. Tetrahedron Lett. 1987, 28, 3183. "Evidence for Electron Transfer in Reactions of Nucleophiles with Optically Active Alkyl Halides. A Challenge to the S_N2 Transition State."

5. Ashby, E.C.; Pham, Tung N. Tetrahedron Lett., 1987, 28, 3197. "The Question of Validity of Using Radical Probes for Determining SET. The Reaction of Alkyl Halides with $LiAlH_4$.

Since the last report period the following papers have been accepted for publication:

1. Ashby, E.C. Accts Chem. Res. (accepted for publication). "Single Electron Transfer, a Major Reaction Pathway in Organic Chemistry. An Answer to Recent Criticisms."

2. Ashby, E.C.; Pham, Tung; Madjdabadi, Amrollah A. J. Org. Chem. (accepted for publication). "Another Challenge to the Validity of the Use of Cyclizable Probes as Evidence for Single electron Transfer in Nucleophilic Aliphatic Substitution. The Reaction of $LiAlH_4$ with Alkyl Iodides."

3. Ashby, E.C.; Oswald, John J. Org. Chem. (accepted for publication). "Concerning the Mechanism of Grignard Reagent Formation. Evidence for Radical Escape and Return to the Surface of Magnesium."

Since the last report period the following papers have been submitted for publication:

1. Ashby, E.C.; Al-Fekri, Dheya M. Organometallics (submitted for publication). "Reactions of Benzotrihalides with Magnesium. Synthetic and Mechanistic Studies."

2. Ashby, E.C.; Pham, Tung N. J. Org Chem. (submitted for publication). "Concerning the Mechanism and Stereochemistry of Hydride Reduction of Epoxides. The Reduction of 1-Phenylcyclohexene Oxide by AlD_3 and $AlDCl_2$."

3. Madjdabadi, Amrollah A.; Pham, Tung; Ashby, E.C. Synthesis (submitted for publication). "A Simple Method for the Conversion of Bridgehead-, Benzyl- and Benzhydryl Alcohols to Their Corresponding Bromides and Chlorides."

4. Madjdabadi, Amrollah A.; Pham, Tung; Ashby, E.C. Synthesis (submitted for publication). "Simple New Reagents for Transhalogenation of Benzyl-, Benzhydryl-, Adamantyl- and Tertiary Halides."

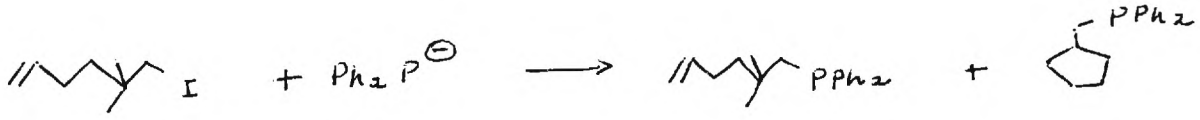
Research in Progress

We have nearly completed a study of the reaction of primary alkyl halides with LDA. We have found that the reaction proceeds via both SET and carbene intermediates. The results of this study have enormous implications and we will be writing up this work soon.

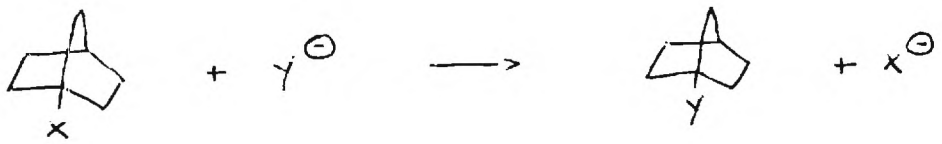
The reaction was studied where X=Cl, Br, I and in different solvents.

We also have nearly completed our work on the reaction of alkyl halides with $LiAlH_4$. This work is summarized in the Communication to be published in J. Org. Chem. shortly.

We have been studying the reaction of alkyl halides (RX where X=Cl, Br, I) with Ph_2PM (where M=Li, Na, K) in various solvents. The work is almost complete. The reactions proceeds by SET; however, maybe even more important is that we have found that the accepted preparation of Ph_2PM compounds does not produce pure compounds. Previous workers have not analyzed the product and it is very impure as determined by ^{31}P NMR. We have developed methods to prepare Ph_2PLi, Ph_2PNa and Ph_2RK in high states of purity.



We are in the midst of a study concerning the reaction of norbornyl halides with the nucleophiles, Me_3Sn^-, Ph_2P^-, PhS^- and $LiAlH_4$ in a variety of solvents.



Since norbornyl halides are not susceptible to S_N2 and S_N1 pathways, evidence is presented for a SET pathway. We also have developed better methods for the preparation of 1-chloro-, 1-bromo- and 1-iodonorbornane.

We have recently begun two studies:

(1) The reaction of $PhCH_2I$, $PhCHI_2$ and $PhCI_3$ with magnesium and with typical nucleophiles in order to determine the S_N1, S_N2, SET and carbene natures of these reactions toward known one electron donors (e.q. Mg) and proposed one electron donors (nucleophiles such as Me_3Sn^-, Ph_2P^-, PhS^- and $LiAlH_4$).

A similar study will be carried out involving a non benzylic system, but involving the same nucleophiles. By such a study it should be possible to show how the mechanism

where X = Cl, Br, I, OTs

of the reaction is a function of the basicity of the nucleophile and the one electron donor characteristics of the nucleophile.

OMB No. 3145-0058
Exp. Date 12/31/85

SUMMARY PROPOSAL BUDGET

FOR NSF USE ONLY

ORGANIZATION	PROPOSAL NO.	DURATION (MONTHS) Proposed	Granted
Georgia Tech Research Corporation			
PRINCIPAL INVESTIGATOR/PROJECT DIRECTOR: E.C. Ashby	AWARD NO.		

A. SENIOR PERSONNEL: PI/PD, Co-PI's, Faculty and Other Senior Associates (List each separately with title, A.6. show number in brackets)	NSF FUNDED PERSON-MOS. CAL.	ACAD	SUMR	FUNDS REQUESTED BY PROPOSER	FUNDS GRANTED BY NSF (IF DIFFERENT)
1. E.C. Ashby			1	$ 8,200	$
2.					
3.					
4.					
5. ( ) OTHERS (LIST INDIVIDUALLY ON BUDGET EXPLANATION PAGE)					
6. ( ) TOTAL SENIOR PERSONNEL (1-5)			1	8,200	
B. OTHER PERSONNEL (SHOW NUMBERS IN BRACKETS)					
1. (2) POST DOCTORAL ASSOCIATES	12			32,000	
2. ( ) OTHER PROFESSIONALS (TECHNICIAN, PROGRAMMER, ETC.)					
3. (1) GRADUATE STUDENTS				11,800	
4. ( ) UNDERGRADUATE STUDENTS					
5. ( ) SECRETARIAL-CLERICAL					
6. ( ) OTHER					
TOTAL SALARIES AND WAGES (A+B)				52,000	
C. FRINGE BENEFITS (IF CHARGED AS DIRECT COSTS)					
TOTAL SALARIES, WAGES AND FRINGE BENEFITS (A+B+C)					
D. PERMANENT EQUIPMENT (LIST ITEM AND DOLLAR AMOUNT FOR EACH ITEM EXCEEDING $1,000.)					
TOTAL PERMANENT EQUIPMENT					
E. TRAVEL 1. DOMESTIC (INCL. CANADA AND U.S. POSSESSIONS)				1,000	
2. FOREIGN					
F. PARTICIPANT SUPPORT COSTS					
1. STIPENDS $					
2. TRAVEL					
3. SUBSISTENCE					
4 OTHER					
TOTAL PARTICIPANT COSTS					
G. OTHER DIRECT COSTS					
1. MATERIALS AND SUPPLIES				12,660	
2. PUBLICATION COSTS/PAGE CHARGES				1,500	
3. CONSULTANT SERVICES					
4. COMPUTER (ADPE) SERVICES					
5. SUBCONTRACTS					
6. OTHER					
TOTAL OTHER DIRECT COSTS				71,875	
H. TOTAL DIRECT COSTS (A THROUGH G)					
I. INDIRECT COSTS (SPECIFY) 60% of total direct costs				43,125	
TOTAL INDIRECT COSTS				43,125	
J. TOTAL DIRECT AND INDIRECT COSTS (H + I)					
K. RESIDUAL FUNDS (IF FOR FURTHER SUPPORT OF CURRENT PROJECTS GPM 252 AND 253)					
L. AMOUNT OF THIS REQUEST (J) OR (J MINUS K)				$115,000	$

PI/PD TYPED NAME & SIGNATURE*	DATE	FOR NSF USE ONLY
E.C. Ashby	11/18/88	INDIRECT COST RATE VERIFICATION
INST. REP. TYPED NAME & SIGNATURE*	DATE	Date Checked / Date of Rate Sheet / Initials - DGC / Program
Lynn Boyd		

NSF Form 1030 (4-83) *Supersedes All Previous Editions*

*SIGNATURES REQUIRED ONLY FOR REVISED BUDGET (GPM 233)

G-33-601

Annual Progress Report (December 1, 1985 - March 30, 1986)

In the 12 months since our last progress report we have published 5 papers. Four of these are full papers in the Journal of Organic Chemistry and one is a Communication in Tetrahedron Letters. All of these papers are concerned with single electron transfer (SET) in organic reactions of major significance. One study was concerned with SET in Aldol Condensation, another with SET in the Meerwein-Ponndorf-Verley reduction, another with SET in reactions of alkyl halides with lithium thiolates and another with the reaction of alkyl halides with $LiAlH_4$. We have another paper accepted for publication concerning SET in metal-halogen exchange; however, this paper has not as yet appeared in print.

List of Publications (December 1, 1985 - November 30, 1986)

(1) E.C. Ashby and J.N. Argyropoulos, "Single Electron Transfer in Aldol Condensation. The Reaction of Lithium Enolates with Diaryl Ketones", J. Org. Chem., 51, 472 (1986).

(2) E.C. Ashby and J.N. Argyropoulos, "Single Electron Transfer in the Meerwein-Ponndorf-Verley Reduction of Benzophenone with Lithium Alkoxides", J. Org. Chem., 51, 3593 (1986).

(3) E.C. Ashby, W.S. Park, A.B. Goel and Wei-Yang Su, "Single Electron Transfer in Reactions of Alkyl Halides with Lithium Thiolates", J. Org. Chem., 50, 5184 (1985).

(4) E.C. Ashby and Tung N. Pham, "The Use of 5-Halocyclooctenes as a Radical Probe. Reactions with Lithium Aluminum Hydride", J. Org. Chem., 51, 3598 (1986).

(5) E.C. Ashby and J.N. Argyropoulos, "Evidence for a Single Electron Transfer Mechanism in the Reduction of Benzophenone with Lithium Alkoxides", Tetrahedron Lett., 27, 465 (1986).

We have completed our work in the areas above and in the area of metal-halogen exchange and are now working in the following areas:

(1) Chiral Probes.

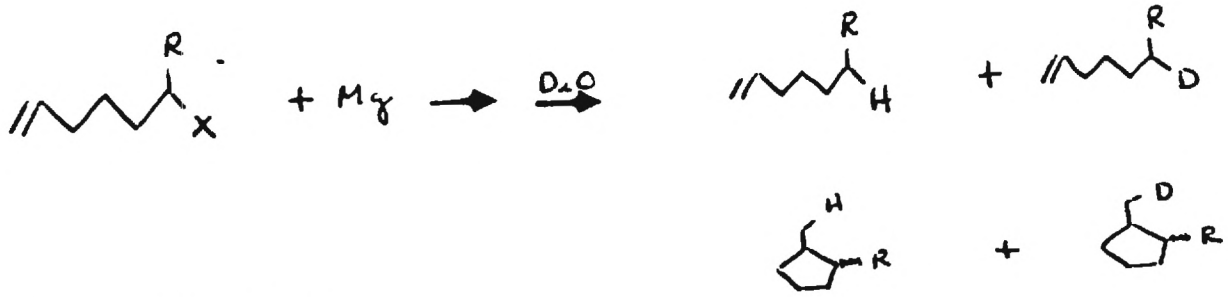
We have nearly completed our studies concerning the reactions of chiral alkyl halides with nucleophiles. The use of chiral halides allows for the determination of radical intermediates in the solvent cage of a nucleophilic aliphatic substitution reaction. Indeed we do have evidence to challenge the

$$\underset{\text{(chiral)}}{R^{*}X} + Y^{-} \longrightarrow \underset{\text{(partially racemic)}}{RY} + X^{-}$$

S_N2 transition state.

Details of Radical Reactions in the Solvent Cage

The reaction of alkyl halides with magnesium in ether is known to be a radical process. We are presently studying the reactions of alkyl halide radical probes with magnesium in several solvents to obtain details as to exactly what is happening in the solvent cage of a radical reaction.

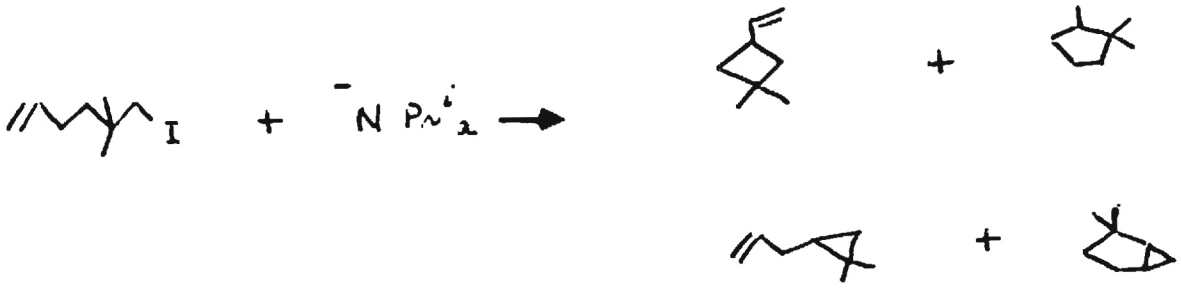


R = H, CH_3 X = Cl, Br, I

Solvent = Et_2O, THF, HMPA

Reaction of Alkyl Halides with NR_2^-

We have nearly completed our study concerning the reaction of an alkyl halide with LDA in order to determine the SET nature of this reaction. We have significant evidence that SET is involved.



Reactions of Norbornyl Halides to Probe Radical Reactions

We are just beginning studies of the reactions of 1-substituted norbornyl halides with nucleophiles as a test for a SET process. Such reactions would

X = OTs, Cl, Br, I

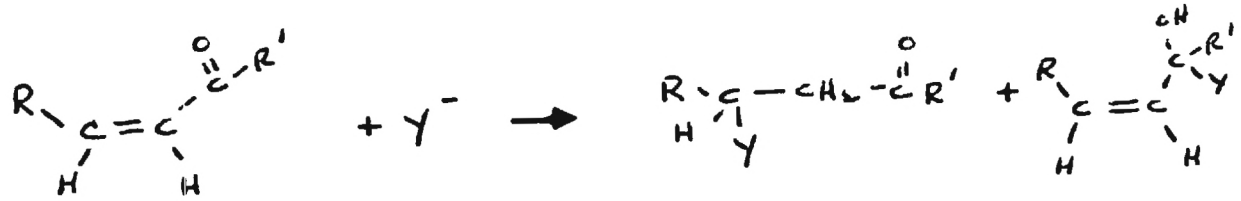
Y^- = PhS^-, Ph_2P^-, Me_3Sn^-

solvent = Et_2O, THF, HMPA

not be expected proceed by S_N1 or S_N2 pathways.

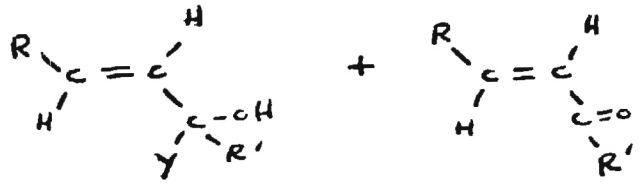
Reactions of Cis-Enones with Nucleophiles

We have prepared three cis-enones in order to test the SET nature of their reactions with nucleophiles. The recovery of trans enone and trans 1,2-



R = t-Bu , Ph

R' = t-Bu , Ph



addition product is an indication of SET. We are about 50% complete in these studies.

Update of Current and Pending Support

The current grant is our only support. No other proposals are pending.

Statement of Residual Research Funds

At present all funds have been expended.

G-33-601

School of Chemistry
(404) 894-4002

Georgia Institute of Technology
Atlanta, Georgia 30332
[illegible] System of Georgia

April 9, 1985

Dr. Donald W. Slocum
Program Director for Inorganic
Chemical Dynamics
Chemical Dynamics Program
National Science Foundation
Washington, D.C. 20550

Dear Don:

Attached is a copy of our NSF Annual Report (June 1, 1984-May 31, 1985). I apologize for being a little late.

We continue to work very hard in the area of Single Electron Transfer Chemistry. To obtain unequivocal conclusions in mechanistic areas is always difficult and this area has been a real challenge.

I hope you will visit us in Atlanta sometime.

Sincerely,

E.C. Ashby
Regents' Professor of Chemistry

slf

Attachment

Single Electron Transfer. A Major Reaction Pathway in Organic Chemistry

In the past year three major research projects were completed and submitted for publication. Two of these projects were begun during this time period (June 1, 1984 - May 31, 1985) and the other project was begun earlier. Two additional projects are in progress, but have not proceeded sufficiently far to report on at this time. During the same time period six publications appeared involving work supported by the NSF. The publications that appeared are as follows:

(1) E.C. Ashby and J.N. Argyropoulos, "Evidence for Single Electron Transfer in the Reaction of a Lithium Enolate with a Primary Alkyl Iodide", Tetrahedron Lett., 25, 7(1984).

(2) E.C. Ashby, R.N. DePriest, A.B. Goel, Bernd Wenderoth and Tung Pham, "Occurence of Electron Transfer in the Reduction of Organic Halides by $LiAlH_4$ and AlH_3," J. Org. Chem., 49, 3545 (1984).

(3) E. C. Ashby and T.N. Pham, "Endo -5-(2-Haloethyl)-2-Norbornene. A New Radical Probe," Tetrahedron Lett., 25, 4333 (1984).

(4) E.C. Ashby, Bernd Wenderoth, Tung Pham and Won-Suh Park," Evidence for Single Electron Transfer in the Reduction of Organic Halides by Lithium Triethylborohydride", J. Org. Chem., 49, 4505 (1984).

(5) E.C. Ashby, R.N. DePriest and Wei-Yang Su, "Electron Transfer in the Reactions of Alkyl Halides with Sodium Trimethyltin", Organometallics, 3, 1718 (1984).

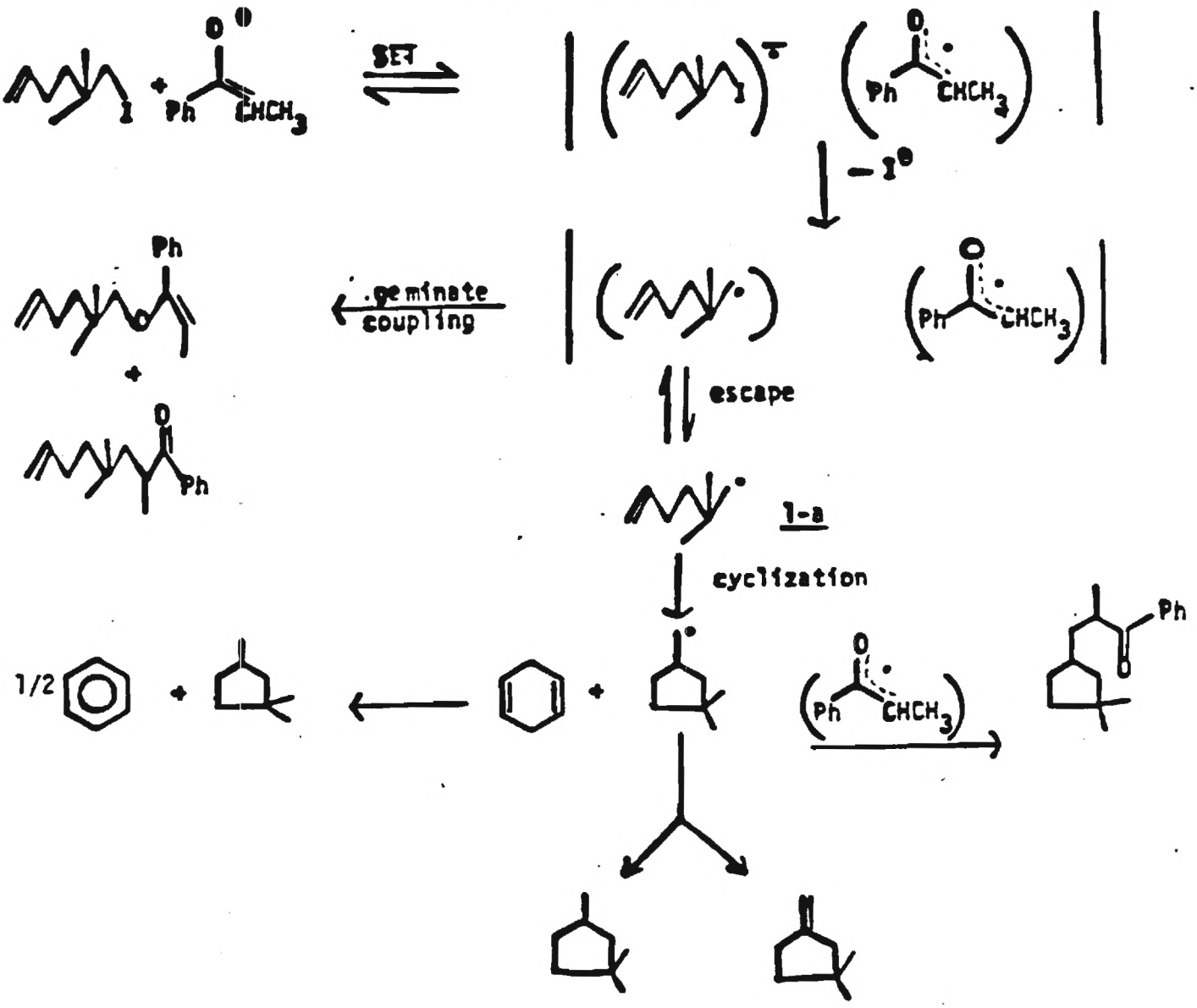
(6) E.C. Ashby, Doug-Hak Bae, Won-Suh Park, Robert N. DePriest and Wei-Yang Su, "Evidence for Single Electron Transfer in the Reactions of Alkoxides with

Alkyl Halides", Tetrahedron Lett., 2825 (1984). The three projects that were completed this report period, but which have not appeared in print, are as follows:

I. Single Electron Transfer in the Reaction of Enolates with Alkyl Halides.

Single Electron Transfer (SET) in the reaction of a model system consisting of lithiopropiophenone with primary neopentyl type alkyl halides and tosylate was investigated by (1) the use of an appropriate cyclizable alkyl halide probe, (2) observing the effect of varying the leaving group on reaction rate and product distribution, (3) studying the effect of light, di-tert-butylnitroxyl radical, and p-dinitrobenzene on the rate of reaction, (4) observing the consequence of varying solvent composition on both the reaction rate and product distribution, and (5) studying the effects of the radical traps, dicyclohexylphosphine and 1,4-cyclohexadiene, on product composition. The results of these studies indicate that single electron transfer is the major reaction pathway involved in the reaction of the enolate with the alkyl iodide in HMPA and that the corresponding bromide and tosylate react by a S_N2 process.

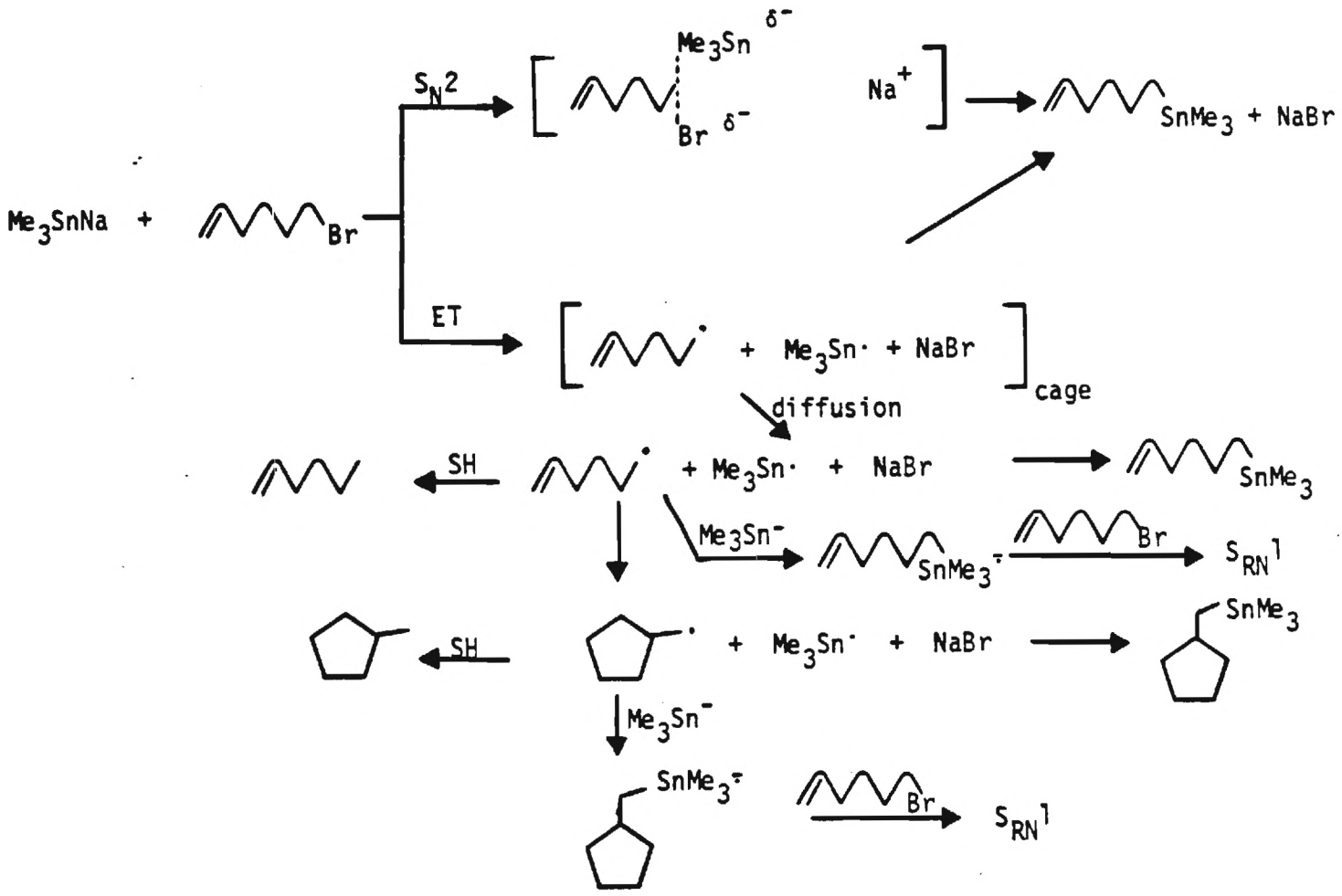
Proposed Mechanism



II. Evidence for Electron Transfer in the Reaction of Sodium Trimethyltin with 1° Alkyl Halides

The reaction of sodium trimethyltin with 1° alkyl halides has been studied in detail with emphasis on the effect of solvent and added radical and carbanion traps. Contrary to previous reports all evidence indicates that the reaction proceeds by an electron transfer process involving radical intermediates for the systems studied.

Proposed Mechanism

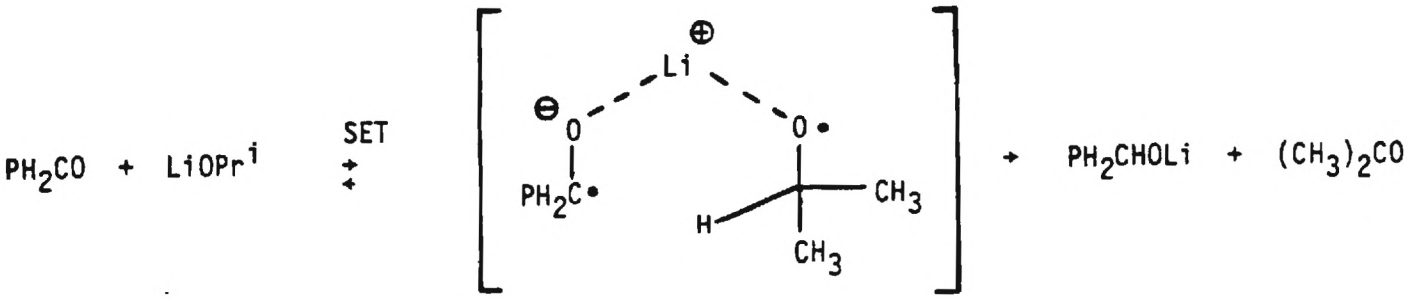


III. Evidence for Electron Transfer in the Reduction of Benzophenone with Lithium Alkoxides

The Meerwein-Ponndorf-Verley reduction of ketones is generally believed to proceed via a polar mechanism. Nevertheless, the reduction of benzophenone by lithium amides and alkoxides have been shown to produce radical intermediates. In addition, stereochemical evidence for a single electron transfer mechanism in the reduction of cyclic ketones with alkoxyaluminium dichlorides has been reported.

We have found that the reduction of benzophenone by lithium isopropoxide gives rise to a paramagnetic intermediate which decays in a first-order fashion and whose first-order rate constant is approximately equal to the pseudo-first-order rate constant for the formation of the product, benzhydrol. The proposed mechanism of reaction is as follows:

Proposed Mechanism



Budget

We anticipate no remaining funds for the present research period

Current Support and Pending Proposals

Our entire work is sponsored by NSF and PRF. Our current PRF grant (# 14102 -AC4-C) is dated from 9/1/82 to 8/31/85. It is a 3 year grant for $45,000. The PRF effort presently involves a study of the mechanism of metal-Halogen Interchange. NSF studies have involved mainly non-organometallic reactions whereas the work suggested by PRF has involved mainly mechanistic studies in the area of organometallic reaction mechanism.

G-33-601

Single Electron Transfer. A Major Reaction Pathway in Organic Chemistry

In the past year three major research projects were completed and submitted for publication. Two of these projects were begun during this time period (June 1, 1984 - May 31, 1985) and the other project was begun earlier. Two additional projects are in progress, but have not proceeded sufficiently far to report on at this time. During the same time period six publications appeared involving work supported by the NSF. The publications that appeared are as follows:

(1) E.C. Ashby and J.N. Argyropoulos, "Evidence for Single Electron Transfer in the Reaction of a Lithium Enolate with a Primary Alkyl Iodide", Tetrahedron Lett., 25, 7(1984).

(2) E.C. Ashby, R.N. DePriest, A.B. Goel, Bernd Wenderoth and Tung Pham, "Occurence of Electron Transfer in the Reduction of Organic Halides by $LiAlH_4$ and AlH_3," J. Org. Chem., 49, 3545 (1984).

(3) E. C. Ashby and T.N. Pham, "Endo -5-(2-Haloethyl)-2-Norbornene. A New Radical Probe," Tetrahedron Lett., 25, 4333 (1984).

(4) E.C. Ashby, Bernd Wenderoth, Tung Pham and Won-Suh Park," Evidence for Single Electron Transfer in the Reduction of Organic Halides by Lithium Triethylborohydride", J. Org. Chem., 49, 4505 (1984).

(5) E.C. Ashby, R.N. DePriest and Wei-Yang Su, "Electron Transfer in the Reactions of Alkyl Halides with Sodium Trimethyltin", Organometallics, 3, 1718 (1984).

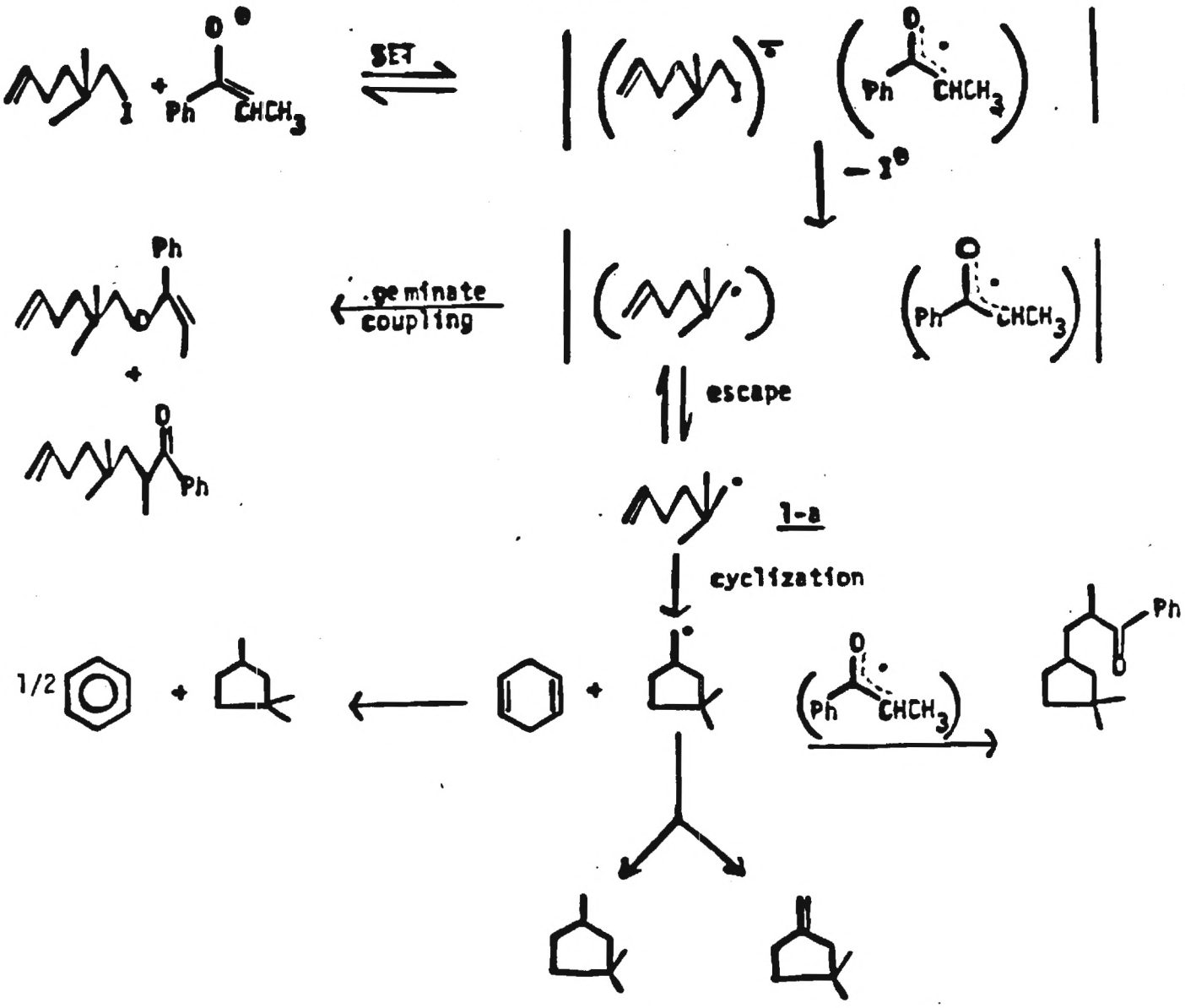
(6) E.C. Ashby, Doug-Hak Bae, Won-Suh Park, Robert N. DePriest and Wei-Yang Su, "Evidence for Single Electron Transfer in the Reactions of Alkoxides with

Alkyl Halides", Tetrahedron Lett., 2825 (1984). The three projects that were completed this report period, but which have not appeared in print, are as follows:

I. Single Electron Transfer in the Reaction of Enolates with Alkyl Halides.

Single Electron Transfer (SET) in the reaction of a model system consisting of lithiopropiophenone with primary neopentyl type alkyl halides and tosylate was investigated by (1) the use of an appropriate cyclizable alkyl halide probe, (2) observing the effect of varying the leaving group on reaction rate and product distribution, (3) studying the effect of light, di-tert-butylnitroxyl radical, and p-dinitrobenzene on the rate of reaction, (4) observing the consequence of varying solvent composition on both the reaction rate and product distribution, and (5) studying the effects of the radical traps, dicyclohexylphosphine and 1,4-cyclohexadiene, on product composition. The results of these studies indicate that single electron transfer is the major reaction pathway involved in the reaction of the enolate with the alkyl iodide in HMPA and that the corresponding bromide and tosylate react by a S_N2 process.

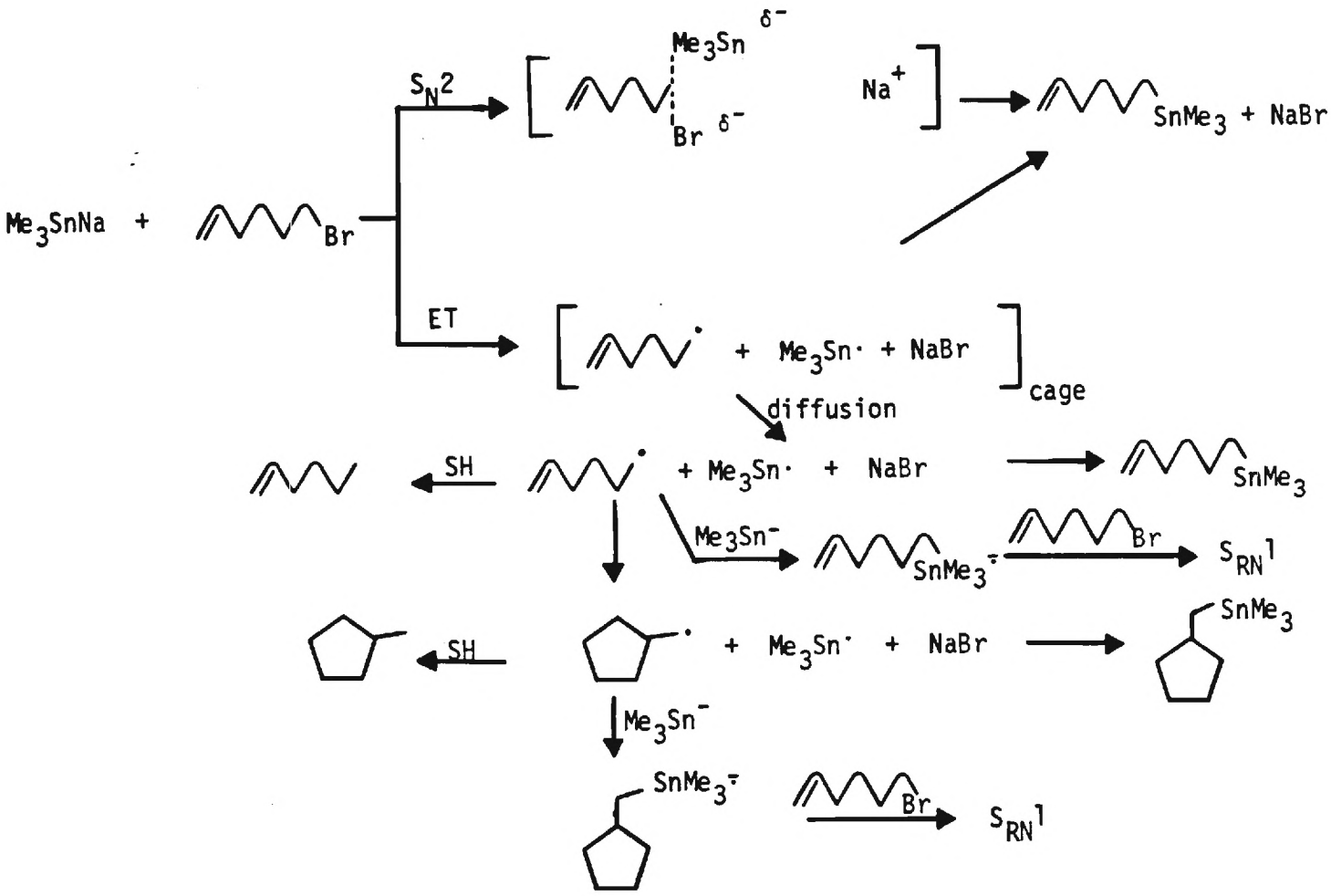
Proposed Mechanism



II. Evidence for Electron Transfer in the Reaction of Sodium Trimethyltin with 1° Alkyl Halides

The reaction of sodium trimethyltin with 1° alkyl halides has been studied in detail with emphasis on the effect of solvent and added radical and carbanion traps. Contrary to previous reports all evidence indicates that the reaction proceeds by an electron transfer process involving radical intermediates for the systems studied.

Proposed Mechanism

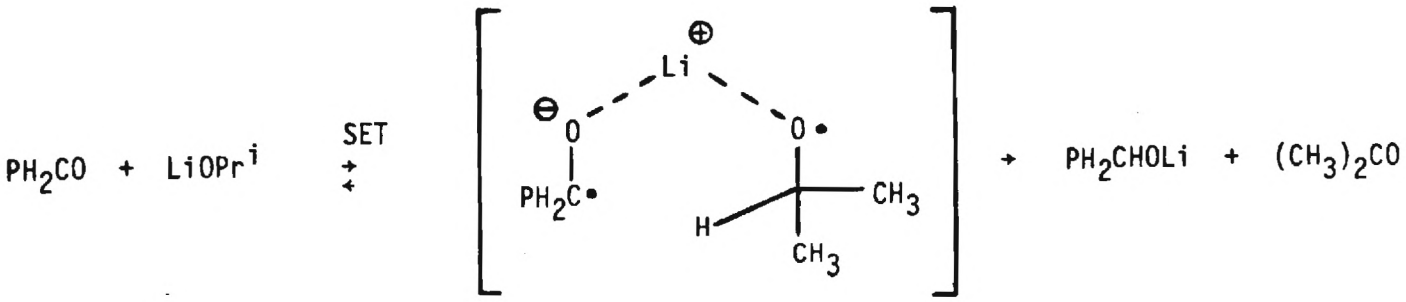


III. Evidence for Electron Transfer in the Reduction of Benzophenone with Lithium Alkoxides

The Meerwein-Ponndorf-Verley reduction of ketones is generally believed to proceed via a polar mechanism. Nevertheless, the reduction of benzophenone by lithium amides and alkoxides have been shown to produce radical intermediates. In addition, stereochemical evidence for a single electron transfer mechanism in the reduction of cyclic ketones with alkoxyaluminium dichlorides has been reported.

We have found that the reduction of benzophenone by lithium isopropoxide gives rise to a paramagnetic intermediate which decays in a first-order fashion and whose first-order rate constant is approximately equal to the pseudo-first-order rate constant for the formation of the product, benzhydrol. The proposed mechanism of reaction is as follows:

Proposed Mechanism



Budget

We anticipate no remaining funds for the present research period

Current Support and Pending Proposals

Our entire work is sponsored by NSF and PRF. Our current PRF grant (# 14102 -AC4-C) is dated from 9/1/82 to 8/31/85. It is a 3 year grant for $45,000. The PRF effort presently involves a study of the mechanism of metal-Halogen Interchange. NSF studies have involved mainly non-organometallic reactions whereas the work suggested by PRF has involved mainly mechanistic studies in the area of organometallic reaction mechanism.

G-33-601

GEORGIA TECH RESEARCH CORPORATION

GEORGIA INSTITUTE OF TECHNOLOGY
ATLANTA, GEORGIA 30332-0420

Telex: 542507 GTRCOCAATL
Fax: (404) 894-3120

Phone: (404) 894-4817

Refer to: LB/02.107.000.86.067

17 January 1986

National Science Foundation
1800 G Street, N.W.
Washington, D. C. 20550

Attention: Dr. Kenneth Kustin
Program Director, Chemical Organics
Chemical Dynamics Program

Subject: Grant No. CHE-8403024; Request for Year Two Incremental Funding for Continuing Grant entitled, "Single Electron Transfer. A Major Reaction Pathway in Organic Chemistry"

Dear Sir:

In accordance with NSF Grant Policies, the GTRC is pleased to submit the Annual Progress Report and Request for Continued Support on the subject research project.

We believe that the enclosed material will provide you with all the necessary information. However, if additional information is required, please contact Dr. Ashby at 404/894-4040 concerning the technical program. Contractual matters should be referred to the undersigned at 404/894-4817.

We appreciate the opportunity of submitting this request and look forward to the possibility of continuing our work with you on this project.

Sincerely,

Lynn Boyd
Contracting Officer

LB/tjm

Addressee: In triplicate
Enclosure: Progress Report - in triplicate
Proposal Budget - in triplicate
Statement of Funds Remaining - in triplicate
Publication Reprints

cc: G-33-601

School of Chemistry
(404) 894-4002

Georgia Institute of Technology
Atlanta, Georgia 30332
A Unit of the University System of Georgia

January 16, 1986

Dr. Kenneth Kustin
Program Director, Chemical Organics
Chemical Dynamic Program
National Science Foundation
Washington, DC 20550

Dear Dr. Kustin,

I thank you very much for your help in getting my NSF grant back on track. I did indeed forget that the reporting date was changed from June 1, 1986 to December 1, 1985 and now realize why I am almost out of funds.

The research is going better than ever as you will see in the second part of the Annual Progress Report.

Sincerely,

E. C. Ashby
Regents' Professor of Chemistry

dgs

OMB No. 3145-0058
Exp. Date 12/31/85

SUMMARY PROPOSAL BUDGET

FOR NSF USE ONLY

ORGANIZATION: GEORGIA TECH RESEARCH CORPORATION

PROPOSAL NO.: | DURATION (MONTHS) Proposed: | Granted:

PRINCIPAL INVESTIGATOR/PROJECT DIRECTOR: E. C. Ashby

AWARD NO.:

A. SENIOR PERSONNEL: PI/PD, Co-PI's, Faculty and Other Senior Associates (List each separately with title; A.6. show number in brackets)	NSF FUNDED PERSON-MOS CAL.	ACAD	SUMR	FUNDS REQUESTED BY PROPOSER	FUNDS GRANTED BY NSF (IF DIFFERENT)
1. Principal Investigator			1.5	$ 10,800	$
2.					
3.					
4.					
5. ( ) OTHERS (LIST INDIVIDUALLY ON BUDGET EXPLANATION PAGE)					
6. (1) TOTAL SENIOR PERSONNEL (1-5)			1.5	10,800	
B. OTHER PERSONNEL (SHOW NUMBERS IN BRACKETS)					
1. (1) POST DOCTORAL ASSOCIATES	12			16,000	
2. ( ) OTHER PROFESSIONALS (TECHNICIAN, PROGRAMMER, ETC.)					
3. (2) GRADUATE STUDENTS				23,000	
4. ( ) UNDERGRADUATE STUDENTS					
5. ( ) SECRETARIAL-CLERICAL					
6. ( ) OTHER					
TOTAL SALARIES AND WAGES (A+B)				49,800	
C. FRINGE BENEFITS (IF CHARGED AS DIRECT COSTS) (21% of A-6 and B-1)				5,628	
TOTAL SALARIES, WAGES AND FRINGE BENEFITS (A+B+C)				55,428	
D. PERMANENT EQUIPMENT (LIST ITEM AND DOLLAR AMOUNT FOR EACH ITEM EXCEEDING $1,000:)					
TOTAL PERMANENT EQUIPMENT					
E. TRAVEL 1. DOMESTIC (INCL. CANADA AND U.S. POSSESSIONS)				700	
2. FOREIGN					
F. PARTICIPANT SUPPORT COSTS					
1. STIPENDS $					
2. TRAVEL					
3. SUBSISTENCE					
4. OTHER					
TOTAL PARTICIPANT COSTS					
G. OTHER DIRECT COSTS					
1. MATERIALS AND SUPPLIES				9,000	
2. PUBLICATION COSTS/PAGE CHARGES				1,195	
3. CONSULTANT SERVICES					
4. COMPUTER (ADPE) SERVICES					
5. SUBCONTRACTS					
6. OTHER					
TOTAL OTHER DIRECT COSTS				10,195	
H. TOTAL DIRECT COSTS (A THROUGH G)				66,323	
I. INDIRECT COSTS (SPECIFY) 55.3% of total direct costs (rate approved for the period 7/1/84 - 6/30/85 and is subject to change pending negotiation.)				36,677	
TOTAL INDIRECT COSTS				103,000	
J. TOTAL DIRECT AND INDIRECT COSTS (H + I)					
K. RESIDUAL FUNDS (IF FOR FURTHER SUPPORT OF CURRENT PROJECTS GPM 252 AND 253)					
L. AMOUNT OF THIS REQUEST (J) OR (J MINUS K)				$ 103,000	$

PI/PD TYPED NAME & SIGNATURE*: E. C. Ashby — DATE: 1/16/86

INST. REP. TYPED NAME & SIGNATURE*: Lynn Boyd — DATE: 1/17/86

FOR NSF USE ONLY
INDIRECT COST RATE VERIFICATION
Date Checked | Date of Rate Sheet | Initials - DGC Program

NSF Form 1030 (4-82) Supersedes All Previous Editions

*SIGNATURES REQUIRED ONLY FOR REVISED

Annual Progress Report (June 1, 1985 - November 30, 1985)

In the six months since our last report period, four publications have appeared in print. These publications are listed separately and only one (halogen-metal exchange) represents work still in progress. The other area in progress is concerned with the use of stereochemical probes to detect electron transfer in nucleophilic aliphatic substitution reactions.

Halogen-Metal Exchange

In the area of halogen-metal exchange we continue to pursue the mechanisms of reactions of organolithium compounds with alkyl halides using radical traps and cyclizable radical probes under many different conditions in an attempt to distinquish between radical and carbanion intermediates in these reactions. Although we recently published a communication in this area, there is much left to do. We have recently prepared $(CD_3)_3CLi$ and $(CH_3CD_2)_2O$ for some important studies that we believe will help us solve some very perplexing problems. Also, we find that this reaction is affected significantly by solvent and the nature of the leaving group (Cl, Br, I).

Chiral Probes

The second area in which we are involved we believe to be of earthshaking importance. We believe that we now have conclusive proof that the most fundamental and classic nucleophilic aliphatic substitution reactions labeled as S_N2 processes are instead SET processes. We have been able to show in the

$$RX + Y^- \longrightarrow RY + X^-$$

reaction of an alkyl halide with a nucleophile (eq. 1) that the radical character of the intermediate can be probed by using optically active alkyl halides and observing the degree of racemization of the product. Tosylates, always, and

chlorides, almost always, produce a product with 100% inversion of configuration whereas the corresponding bromide and iodide produce the product with less than 90% inversion of configuration. This kind of sensitive probe can detect radical character in the solvent cage whereas the typical cyclizable radical probes such as 5-hexenyl halides, as well as trapping agents, can only produce positive results when the radical escapes the solvent cage. Now we have a probe that will detect radical intermediates in the solvent cage. We are working very hard in this area.

List of Publications (June 1- November 30, 1985)

1. E. C. Ashby, Tung N. Pham and Bonjin Park, "Evidence for Electron Transfer in Metal-Halogen Exchange. The Reaction of Organolithium Compounds with Alkyl Halides," Tetrahedron Lett, 26, 4691 (1985).

2. Yunshi Zhang, Bernd Wenderoth, Wei-Yang Su and E. C. Ashby, "New Methodology in Determining Evidence for Single Electron Transfer in the Reactions of Grignard Reagents with Ketones", J. Organometal. Chem., 292, 29 (1985).

3. E. C. Ashby and John Argyropoulos, "Single Electron Transfer in the Reactions of Enolates with Alkyl Halides," J. Org. Chem., 50, 3274 (1985).

4. E. C. Ashby, Wei-Yang Su and Tung N. Pham, "Evidence of Electron Transfer in the Reactions of (Trimethylstanyl) Sodium with Primary Alkyl Halides, Organometallics, 4, 1493 (1985).

Update of Current and Pending Support

The current grant, NSF grant CHE-8403024, is our only current support. No other grants are pending and there are currently no plans to submit a proposal to other agencies.

Statement of Residual Research Funds

The current grant in 86.3% expended. The remaining money is earmarked to support two postdoctoral assistants concurrently who will arrive soon. Since this expenditure is at a higher rate than the grant could usually handle, therefore we have accumulated money in personal services to handle this future expenditure.

Reprinted from Organometallics, 1985, 4, 1493.

Evidence for Electron Transfer in the Reaction of (Trimethylstannyl)sodium with Primary Alkyl Halides

E. C. Ashby,* Wei-Yang Su, and Tung N. Pham

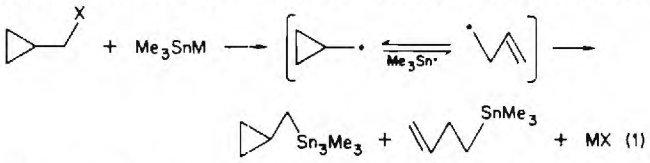
School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

Received August 21, 1984

The reaction of (trimethylstannyl)sodium with primary alkyl halides has been studied in detail with emphasis on the effect of solvent and added radical and carbanion traps. Contrary to previous reports all evidence indicates that the reaction proceeds by an electron-transfer process involving radical intermediates for the systems studied.

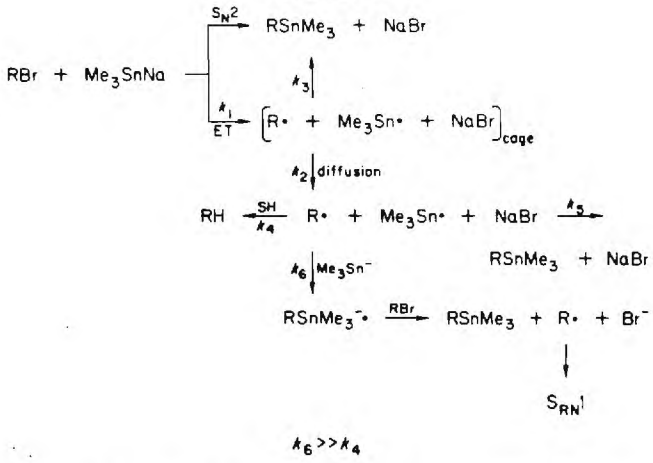
Introduction

In recent years several mechanisms have been proposed for the formation of tetraalkyltin compounds by the reaction of organic halides with triorganostannyl alkali-metal compounds.[1] These proposals were based on a variety of stereochemical studies,[2-4] a variety of experiments in which intermediates were trapped,[5,6] and a formation of rearranged products.[7-9] The three basic mechanistic pathways which have been described are (a) a classic S_N2 substitution of the alkyl halide with a trialkylstannyl anion as the nucleophile, (b) substitution by an electron-transfer (ET) process, and (c) substitution by halogen–metal exchange (HME). San Filippo[7,8] has reported that trimethylstannyl anion yielded rearranged products on reaction with cyclopropylcarbinyl bromide and iodide and suggested the intermediacy of free radicals in this reaction (eq 1).

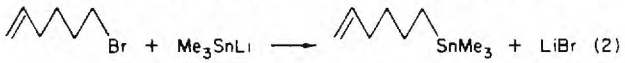


However, Newcomb[10] found no evidence for an electron-transfer pathway in the reaction of 6-bromo-1-hexene with

Scheme I



(trimethylstannyl)lithium in that only straight chain tetraalkyltin product was formed (eq 2), and hence these



results presented a challenge to the findings of San Filippo. Moreover, Kuivila[11] reported that reactions of (trimethylstannyl)sodium (1) with unhindered primary halides proceed exclusively by an S_N2 pathway. With a very sterically hindered primary bromide (neopentyl bromide), significant reaction by an ET pathway (32%) was found in reactions involving Me_3SnNa. Kuivila also studied the cyclopropylcarbinyl–trimethylstannyl alkali systems previously reported by San Filippo by the technique of

(1) Kuivila, H. G. *Ann. N.Y. Acad. Sci.* **1974**, *239*, 315.
(2) Jensen, F. R.; Davis, D. D. *J. Am. Chem. Soc.* **1971**, *93*, 4047.
(3) Kuivila, H. G.; Considine, J. L.; Kennedy, J. D. *J. Am. Chem. Soc.* **1972**, *94*, 7206.
(4) Bock, P. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 2826.
(5) Kuivila, H. G; DiStefano, F. V. *J. Organomet. Chem.* **1976**, *122*, 171.
(6) Wursthorn, K. R.; Kuivila, H. G.; Smith, G. F. *J. Am. Chem. Soc.* **1978**, *100*, 2779.
(7) San Filippo, J., Jr.; Silberman, J.; Fagan, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 4834.
(8) San Filippo, J., Jr.; Silberman, J. *J. Am. Chem. Soc.* **1982**, *104*, 2831.
(9) Alnajjar, M. S.; Kuivila, H. G. *J. Org. Chem.* **1981**, *46*, 1053.
(10) Newcomb, M.; Courtney, A. R. *J. Org. Chem.* **1980**, *45*, 1707.
(11) Smith, G. F.; Kuivila, H. G.; Simon, R.; Sultan, L. *J. Am. Chem. Soc.* **1981**, *103*, 833. Professor Kuivila at a recent meeting reported to E. C. Ashby that he has recently obtained evidence of electron transfer in the reaction of Me_3SnNa with a primary alkyl halide.

0276-7333/85/2304-1493$01.50/0

Table I. Reaction of Primary Alkyl Bromides with (Trimethylstannyl)sodium (1) in the Presence of Radical Traps[a]

entry	substrate	additive,[b] molar equiv	time, min	yield of product,[b] % RBr	yield of product,[b] % $RSnMe_3$	yield of product,[b] % RH
1	*n*-BuBr (**4**)	none	1	0	100	...
2	**4**	**2**, 0.27	1.5	31.4	67.7	...
3	**4**	**3**, 0.20	1.5	0	91.8	...
4	**4**	**2**, 0.27	15	0	99.0	...
5	$(CH_3)_2CHCH_2Br$ (**5**)	none	2	0	98.0	...
6	**5**	**2**, 0.26	5	50.4	47.9	...
7	**5**	**3**, 0.28	6	0	86.3	...
8	$CH_3(CH_2)_3CH(C_2H_5)CH_2Br$ (**6**)	none	2	0	96.4	1.5
9	**6**	**2**, 0.19	5	78.7	18.0	trace
10	**6**	**2**, 0.39	6	98.9	2.1	0
11	**6**	**3**, 0.28	6	0	85.4	<1

[a] Reactions were conducted by using 0.15 M concentration of bromide and 0.30 M concentration of **1** at 0 °C in THF. [b] Based on bromide.

trapping the intermediates and by the study of counerion effects. On the basis of the results of this work, Kuivila[12] reported that formation of rearranged products in reactions of cyclopropylcarbinyl halides should not be taken as prima facie evidence for kinetically free radical intermediates. Nevertheless, we have found in recent work[13] that ET is the major pathway of the reaction of Me_3SnNa with secondary alkyl bromides and a radical anion scavenger [*p*-dinitrobenzene (**2**)] and a free radical scavenger [di-*tert*-butylnitroxyl radical (**3**)] does indeed trap the radical anion and free radical, respectively, and thus slows down the rate of reaction. In the above reaction the primary radical, formed after secondary radical diffusion out of the solvent cage followed by subsequent cyclization, reacts with Me_3Sn^- to start the $S_{RN}1$ radical chain process. Since secondary alkyl halides can react with Me_3SnNa via an ET pathway, we were anxious to determine if Me_3SnNa will also react with primary alkyl halides by a similar pathway. Previous results can be explained by assuming that the substitution product is formed inside the solvent cage or outside the solvent cage assuming that the rate of straight chain radical trapped by Me_3Sn^- (or $Me_3Sn\cdot$) is much faster than the rate of radical cyclization or radical trapping by solvent or DCPH. Our suggestion that explains all of the data obtained so far by ourselves and others is described in Scheme I. R· can of course cyclize after diffusion from the solvent cage to produce $R_c\cdot$ which can then do all of the same things shown for R·.

We would now like to report our studies which indicate that free radicals are formed as intermediates in the reaction of primary alkyl halides with Me_3SnNa.

Results and Discussion

Studies with Primary Alkyl Bromides. We have examined the reaction of primary alkyl bromides with Me_3SnNa in the presence of a radical anion scavenger [*p*-dinitrobenzene (**2**)] and a radical scavenger [di-*tert*-butylnitroxyl radical (**3**)] and the results are given in Table I. With *n*-butyl bromide (**4**), the yield of substitution product is decreased from 100% to 67.7% (entries 1 and 2) in the presence of 27 mol % of **2** in the same time period. Moreover, this reaction will proceed to completion even in the presence of **2** if it is allowed to proceed long enough (entry 4). Furthermore, we have found that increasing the steric requirement of the primary alkyl bromide results in a more effective retardation of the reaction rate on addition of **2** (compare entries 5, 6, 8, 9, and 10). These results show that these reactions are inhibited by adding **2** and that the $S_{RN}1$ chain process involving a radical anion participates in the reaction of primary alkyl bromides with Me_3SnNa. However, the reactions of primary alkyl bromides with Me_3SnNa still proceed completely in the presence of **3** (see entries 3, 7, and 11) with the only effect that the yield of substitution product is decreased. Interestingly, a significant amount of byproduct identified (GC–MS) as the corresponding di-*tert*-butylnitroxyl alkane is formed in each reaction. Control experiments were carried out and showed that di-*tert*-butylnitroxyl radical does not react with the starting bromides. These results indciate that radical intermediates are involved in the reactions of primary alkyl bromides with Me_3SnNa and that perhaps different inhibitors show different sensitivities to this radical chain process. Nevertheless, these results indicate that in proceeding to a more hindered bromide, less S_N2 character is observed and a higher degree of the ET pathway is involved.

Next, the reactions of 2-ethylhexyl bromide (**6**) with Me_3SnNa were examined in different solvent systems in order to obtain further evidence concerning the radical intermediates involved in the reaction (Table II). It is known that radicals diffuse out of the solvent cage during reaction to a higher extent as the viscosity of the solvent decreases, therefore one would expect to observe more hydrocarbon product in a less viscous solvent as a result of hydrogen abstraction from the solvent as a result of increased radical diffusion from the solvent cage. Therefore, if a reaction proceeds via an ET pathway, the product distribution (substitution product vs hydrocarbon) should depend on the viscosity of the solvent. In addition to this effect, Kuivilla[12,14] has shown that a decrease in cation coordinating ability of the solvent increases the extent of the ET pathway in competition with the S_N2 pathway. Therefore, a more viscous, nonpolar solvent (i.e., *n*-dodecane) and a less viscous, nonpolar solvent (i.e., *n*-pentane) have been used as a cosolvent with THF separately in order to examine the viscosity effect in competition with the cation chelating effect of the solvent in the reaction of **1** with **6**. Entries 1, 2, and 3 represent the reactions of Me_3SnNa with **6** in THF. Dicyclohexylphosphine (DCPH) is a radical and carbanion trap; however, the yields of substitution and hydrocarbon product are unaffected by the carbanion trap *tert*-butylamine (TBA). Entries 4, 5, and 6 show that with a solvent system of lower viscosity (THF, $\eta(0\ °C) = 0.608$; THF–Et_2O $\eta(0\ °C) = 0.466$), the reaction of Me_3SnNa with **6** produces a substantially larger amount of hydrocarbon (14.6%) in the absence of additive, and the amount of hydrocarbon is increased from 14.6% to 40% by the presence of the radical trap DCPH. How-

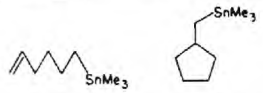
(12) Alnajjar, M. S.; Smith, G. F.; Kuivila, H. G. *J. Org. Chem.* **1984**, *49*, 1271.
(13) Ashby, E. C.; DePriest, R. N.; Su, W.-Y. *Organometallics* **1984**, *3*, 1718.
(14) Alnajjar, M. S.; Kuvila, H. G. *J. Am. Chem. Soc.* **1985**, *107*, 416 (published after manuscript submission).

Table II. Solvent Effects in the Reaction of 2-Ethylhexyl Bromide (6) with (Trimethylstannyl)sodium (1)[a,b]

entry	concn,[c] M	additive,[c] molar equiv	solv (ratio)	yield of product,[c] % $RSnMe_3$	yield of product,[c] % RH
1	0.15	none	THF	96.4	1.5
2	0.15	DCPH, 2	THF	89.3	7.6
3	0.15	TBA, 10	THF	96.1	1.2
4	0.07	none	THF-Et_2O (1:1)	84.2	14.6
5	0.07	DCPH, 2	THF-Et_2O (1:1)	63.8	40.0
6	0.07	TBA, 10	THF-Et_2O (1:1)	81.9	14.8
7	0.07	none	THF-C_5H_{12} (1:1)	91.0	8.1
8	0.07	DCPH, 2	THF-C_5H_{12} (1:1)	70.2	27.1
9	0.07	TBA, 10	THF-C_5H_{12} (1:1)	88.9	9.7
10	0.07	none	THF-$C_{12}H_{26}$ (1:1)	95.1	3.2
11	0.07	DCPH, 2	THF-$C_{12}H_{36}$ (1:1)	73.9	24.5
12	0.07	TBA, 10	THF-$C_{12}H_{26}$ (1:1)	95.0	2.7

[a] Reactions were conducted at 0 °C for 15 min. [b] A twofold excess of 1 was used in each reaction. [c] Based on bromide.

Table III. Reaction of 6-Bromo-1-hexene (7) with Me_3SnNa (1)[a]

entry	additive,[b] molar equiv	solv (ratio)	yield of product,[b] % 			
1	none	THF	99	0	0	0
2	none	THF-Et_2O (1:1)	89.9	8.2	<1	<1
3	DCPH, 5	THF-Et_2O (1:1)	81.6	4.2	7.6	3.1
4	TBA, 10	THF-Et_2O (1:1)	88.4	8.6	<1	<1
5	none	THF-pentane (1:1)	90.7	8.6	<1	<1
6	DCPH, 5	THF-pentane (1:1)	84.1	6.4	5.0	2.0
7	TBA, 10	THF-pentane (1:1)	90.9	8.7	<1	<1
8	none	THF-dodecane (1:1)	96.0	2.1	...	...
9	DCPH, 5	THF-dodecane (1:1)	96.8	>1	1.5	...
10	TBA, 10	THF-dodecane (1:1)	96.2	>0	...	...
11	18-crown-6, 4	THF-Et_2O (1:1)	99.0	0	0	0

[a] Reactions were conducted by using 0.15 M concentration of bromide and 0.30 M concentration of Me_3SnNa at 0 °C for 15 min. [b] Based on the halide.

ever, in the presence of the carbanion trap TBA, the result was similar to that observed in the absence of any additive. Clearly, the hydrocarbon products have a radical precursor and are formed by the abstraction of hydrogen from the solvent and DCPH by the radical.[11] These results are consistent with both a cation chelating effect (THF-Et_2O more poorly coordinates cations than pure THF) and a viscosity effect since a higher degree of radical pathway is indicated at the lower viscosity. Entries 7, 8, and 9 represent the results obtained by using the solvent system (THF-pentane, η(0 °C) = 0.404) of approximately the same viscosity as THF-Et_2O (η(0 °C) = 0.466) in an attempt to separate the cation chelation and solvent viscosity effects. It is clear that the products due to radical intermediates have decreased substantially indicating that cation chelation is quite important. However, it should be pointed out that Et_2O would be expected to be a better radical trap than pentane and thus part of the difference between the THF-Et_2O and the THF-pentane results can be explained on this basis. If indeed cation chelation alone is important, then changing the viscosity of the solvent without changing the cation chelation ability should not result in any change in the products formed from radical precursors. The data show that as the viscosity of the solvent is increased (THF-dodecane, η(0 °C) = 1.072), the products of radical precursors (RH) decrease from 8.1, 27.1, and 9.7% (entries 7–9) to 3.2, 24.5, and 2.7% (entries 10–12), respectively. The difference is not overwhelming, but it is significant. Once again the results of the experiments using TBA (entries 6 and 9) show that carbanions are not trapped in these reactions. It is of course also possible that the effect of solvent may be due to a change in $\Delta(\Delta G^{\ddagger})$ for the S_N2 and ET steps in Scheme I or to the competition between the S_N2 and $S_{RN}1$ process.

Studies with Cyclizable Probes. In order to obtain more mechanistic information, two cyclizable radical probes were used to study the reaction of primary alkyl halides with Me_3SnNa. The results of experiments involving 6-bromo-1-hexene (7) as the cyclizable primary alkyl halide probe are given in Table III. Since the tetraalkyltin compound containing the cyclized moiety derived from the primary alkyl halide probe is most reasonably attributed to the cyclization of an intermediate radical, the percentage of cyclized tetralkyltin compound and both straight chain and cyclized hydrocarbon can be assumed to indicate the minimum extent of reaction proceeding with radical involvement along the reaction pathway.

Entries 2, 3, and 4 of Table III show that in THF-Et_2O (1:1) solvent, the reaction of Me_3SnNa with 7 produces a substantial amount of cyclized substitution product (8.2%) in the absence of DCPH and cyclized substitution product is decreased (from 8.2% to 4.2%) by the presence of DCPH with an increase in hydrocarbon (1–10%). Similar results are obtained in the reaction using THF-pentane (1:1), a solvent system of comparable viscosity to THF-Et_2O (1:1) (entries 5, 6, and 7, Table III). In THF-*n*-dodecane (1:1), a solvent of higher viscosity than THF-Et_2O or THF-pentane, only a small amount of cyclized substitution product (2.4%) was found in the absence of DCPH (entry 8). However, in the presence of DCPH (entry 9), the amount of uncyclized hydrocarbon increased slightly and the amount of cyclized substitution product decreased from 2.1% to only a trace. In the presence of TBA, the result was similar to that observed in the absence of any additive. Interestingly, in THF-Et_2O (1:1), in the

Scheme II

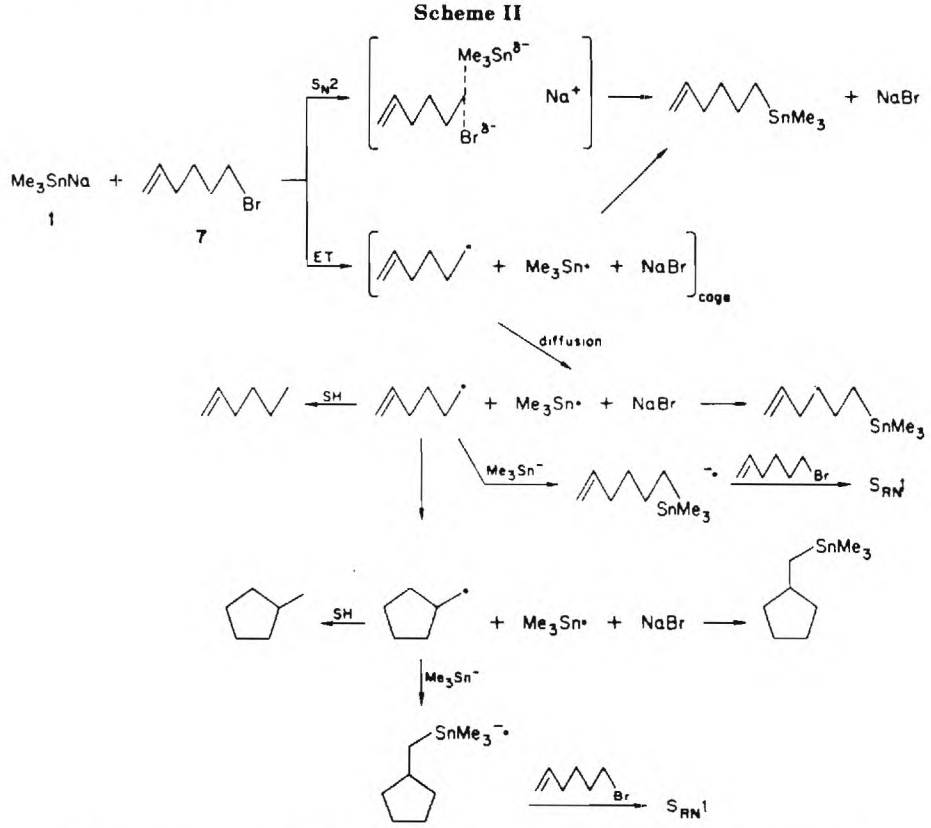


Table IV. Reaction Profile of Me_3SnNa (1) with 6-Bromo-1-hexene (7)[a]

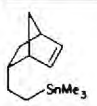
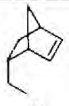
		yield of product,[b] %			
entry	solv (ratio)				
1	THF-$C_{12}H_{26}$ (2:8)	92.2	6.7	···	···
2	THF-$C_{12}H_{26}$ (3:7)	94.1	4.6	···	···
3	THF-$C_{12}H_{26}$ (5:5)	95.5	2.3	···	···
4	THF-$C_{12}H_{26}$ (7:3)	98.0	trace	···	···
5	THF-$C_{12}H_{26}$ (9:1)	98.8	0	···	···
6	THF-Et_2O (2:8)	86.4	12.6	trace	···
7	THF-Et_2O (3:7)	93.5	5.2	···	···
8	THF-Et_2O (5:5)	98.8	trace	···	···
9	THF-Et_2O (7:3)	98.5	0	···	···
10	THF-Et_2O (9:1)	99.1	0	···	···
11	THF-C_5H_{12} (2:8)	83.4	15.1	trace	···
12	THF-C_5H_{12} (3:7)	89.9	9.0	trace	···
13	THF-C_5H_{12} (5:5)	95.0	4.0	···	···
14	THF-C_5H_{12} (7:3)	98.7	trace	···	···
15	THF-C_5H_{12} (9:1)	98.5	0	···	···

[a] Reactions were conducted by using 0.024 M concentrations of bromide and 0.048 M concentrations of Me_3SnNa at 0 °C for 15 min. [b] Yields are based on the halide.

presence of 18-crown-6, the reaction of 1 and 7 produced no cyclized substitution product (entry 11) whereas in the absence of 18-crown-6, 8.2% (entry 2) was produced. Also of interest is the comparison of cyclized substitution product reported in entries 1, 2, 5, and 8 which clearly establishes the importance of viscosity of the solvent in the observation of radical intermediates outside of the solvent cage. In summary, all of these data (Table III) indicate that cyclization of radicals take place outside of the solvent cage, more radicals form in a solvent of lower cation coordinating ability, and more radicals can diffuse out of the solvent cage in a solvent of lower viscosity (THF–Et_2O or THF–pentane) than one of higher viscosity (THF–dodecane) resulting in a greater chance to form cyclized substitution product and cyclized hydrocarbon (trapped by DCPH or solvent as in Scheme II). In addition, TBA shows no effect on the product ratio indicating that carbanion intermediates are not involved in the reaction.

Furthermore, we sought to gain additional insight into the cation chelating effect and viscosity effect of the reaction of 1 with 7 by examining the reaction profile as a function of solvent ratio. The results are shown in Table IV. In all cases, no matter what solvent system was used, the results indicate that the higher extent of ET pathway is observed as the percentage of poor coordinating solvents (Et_2O, pentane, dodecane) is increased. More interestingly, in the case of Et_2O, which is a better cation complexing solvent than *n*-dodecane and also a less viscous solvent than *n*-dodecane, the amount of cyclized substitution

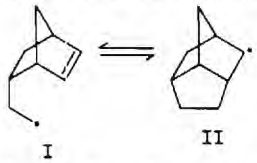
Table V. Reaction of *endo*-5-(2-Bromoethyl)-2-norbornene (8) with Me_3SnNa (1)[a]

entry	additive,[b] molar equiv	solv (ratio)	yield of product,[b] % 	 10	 11
1	none	THF	99.0	0.8	1.0
2	DCPH, 10	THF	86.0	9.6	3.2
3	TBA, 10	THF	99.0	0	<1
4	none	THF-Et_2O (1:1)	98.0	0	4.0
5	DCPH, 10	THF-Et_2O (1:1)	63.0	31.2	10.2
6	TBA, 10	THF-Et_2O (1:1)	98.0	0	3.2
7	none	THF-pentane (1:1)	95.0	0	1.0
8	DCPH, 10	THF-pentane (1:1)	61.0	20.0	19.0
9	TBA, 10	THF-pentane (1:1)	96.0	0	4.7

[a] Reactions were conducted by using 0.05 M concentration of bromide and 0.10 M concentration of Me_3SnNa at 0 °C for 15 min. [b] Based on bromide.

product is greater than it is in the case of *n*-dodecane. If only cation complexation is important, then THF–Et_2O should have produced less cyclization product than THF–dodecane; however, it produced more (12.6% vs. 6.7%). On the other hand, if viscosity is also important, then THF–dodecane would be expected to produce less cyclization product since THF–dodecane is more viscous than THF–Et_2O. Additionally, THF–pentane gave approximately the same results as THF–Et_2O. Since both THF–pentane and THF–Et_2O have approximately the same viscosity, this result is not surprising if viscosity is important. Once again THF–Et_2O is a better cation coordinating solvent than THF–pentane so that if only cation coordination is important, THF–Et_2O should have produced significantly less cyclized substitution product than THF–pentane; and it did not.

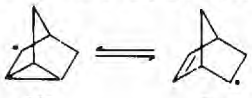
Next, we examined the reaction of Me_3SnNa with a new radical probe, *endo*-5-(2-bromoethyl)-2-norbornene[15] (8) and the results are presented in Table V. We have found that this probe cyclizes approximately 100 times faster than 6-bromo-1-hexene. In general, these results are in good agreement with the previous study which indicates that primary alkyl bromides react with Me_3SnNa by an ET pathway to a significant degree except that significantly higher percentages of radical products are detected using this probe (experiments 5 and 8). A unique aspect of the data reported in Table V is that in no case is there any cyclized substitution product formed. This can be explained on the basis that alkyl radicals diffuse from the solvent cage to form the more stable secondary-alkyl radical which should react with trimethyltin anion (or radical) more slowly than a primary alkyl radical because of increased steric hindrance; hence, more hydrocarbon is produced. This is more easily rationalized if there is an equilibrium between the two radicals I and II (eq 3). This



(3)

I II

is not unexpected since Kuivilla[9] has reported an equilibrium involving the intermediate radicals III and IV found in the reactions of the 5-halo-2-norbornenes and 3-halonortricyclenes with 1 (eq 4). Therefore, the yield



(4)

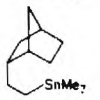
III IV

of cyclized and straight chain hydrocarbon products 10 and 11 should be increased on addition of DCPH. Furthermore, the yield of uncyclized hydrocarbon 10 is decreased from 31% to 20% and cyclized hydrocarbon 11 is increased from 10% to 19% by changing the solvent from THF–Et_2O to THF–pentane (entries 5 and 8). These results suggest that the cyclization of radicals takes place outside the solvent cage and that the straight chain radicals have more chance to be trapped in THF–Et_2O compared to THF–pentane because Et_2O is a better hydrogen atom donor than pentane.

Studies with a Primary Alkyl Iodide. In earlier work[11] Kuivilla showed that primary alkyl iodides react with Me_3SnNa by both S_N2 (65%) and HME (32%) pathways but found no evidence for ET. Now, we have examined the reaction of the new probe *endo*-5-(2-iodoethyl)-2-norbornene (9) with Me_3SnNa, and the results are given in Table VI. With this iodide both 10 (7.3%) and 11 (2.6%) were formed in the absence of a trap (entry 1). The yield of substitution product decreased (from 90.5% to 60.0%) in the presence of 10 molar equiv DCPH with an increase in 10 (from 7.3% to 14.1%) and 11 (from 2.6% to 25.3%) (entry 3). The presence of 10 TBA caused an increase in the yield of 10 to 22.3% (entry 5). The combined traps show that the yields of both 10 and 11 are increased to 33.0% and to 19.0%, respectively (entry 6). Since TBA is known to trap carbanions efficiently,[11] these results indicate that at least 22% of the reaction proceeds via a carbanion intermediate, and since 10 DCPH + 10 TBA produced 52% hydrocarbon, it is clear that at least half of the hydrocarbon produced had a radical precursor. When the reaction of Me_3SnNa with 9 was carried out in the presence of 2 (*p*-dinitrobenzene) and 3 (di-*tert*-butylnitroxyl radical) separately, the rate of reaction was affected by these scavengers. Expectantly, these results suggest that three basic mechanistic pathways (S_N2, HME, and ET) are involved in the reaction of Me_3SnNa with 9 (Scheme III).

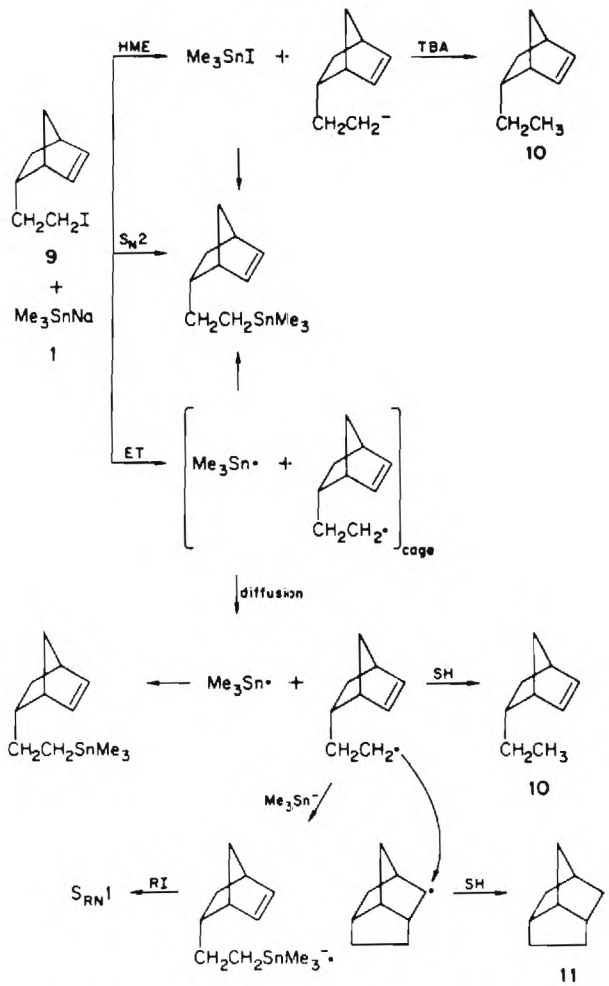
Unexpectantly, no 11 is formed in the presence of TBA (entry 5). It is possible that TBA is a better cation complexing agent than THF and the S_N2 process becomes more favorable. This view is based on the fact that 2.6% of 11 was found in pure THF (entry 1), some of which should have a radical precursor, yet none of 11 was found when 10 molar equiv of TBA was used. If that much TBA changed the course of the reaction to be more S_N2-like because of increased cation complexing by TBA, then the above result is easily understood. Furthermore, the earlier data involving the bromide show that when the reaction proceeds via an ET pathway, two hydrocarbon products

Table VI. Reaction of *endo*-5-(2-Iodoethyl)-2-norbornene (9) with Me_3SnNa (1)[a]

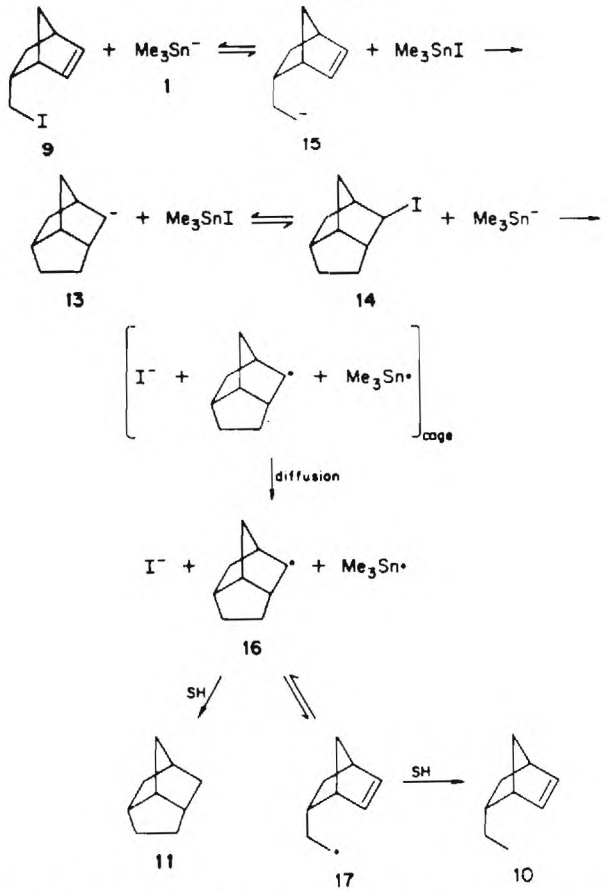
entry	additive,[b] molar equiv	temp, °C	yield of product,[b] %		
					
				10	11
1	none	0	90.5	7.3	2.6
2	DCPH, 1	0	51.5	20.1	30.0
3	DCPH, 10	0	60.0	14.1	25.3
4	TBA, 1	0	75.3	15.0	5.2
5	TBA, 10	0	75.0	22.3	0
6	DCPH, 10; TBA, 10	0	48.6	33.0	19.0
7	none	−23	96.0	3.0	3.5
8	DCPH, 10	−23	80.0	7.4	14.2
9	TBA, 10	−23	95.0	3.0	0.5
10	none	−78	97.0	0	0
11	DCPH, 10	−78	90.0	2.7	2.0
12	TBA, 10	−78	96.0	trace	trace

[a] Reactions were conducted by using 0.05 M concentration of iodide and 0.1 M concentration of Me_3SnNa in THF for 15 min. [b] Based on iodide.

Scheme III



Scheme IV



are formed in a ratio of 3:1 (10:11) in THF in the presence of DCPH (entry 2, Table V). This ratio is different from the ratios observed with the iodide (entries 3 and 6, Table VI). It seems therefore that there must be another pathway in addition to the pathways shown in Scheme III that would be particularly open to reactions with iodide that would result in a higher ratio of cyclized to uncyclized hydrocarbon. It turns out that the carbanion **15** can cyclize to **13** and then a second HME process can occur followed by ET between the new secondary iodide **14** and **1** (Scheme IV). Therefore, DCPH is able to trap the intermediate radical **16** that is produced not only from radical but also from carbanion **13**, and thus the higher ratio of cyclized to uncyclized hydrocarbons for iodides vs. bromides is explained. Of course, part of the hydrocarbon products come from carbanion trapped by DCPH. In the presence of DCPH and TBA (entry 6) the amount of cyclized hydrocarbon is greater than expected since no cyclized hydrocarbon was produced in the presence of 10 TBA alone (entry 5). Possibly DCPH has made TBA a weaker proton donor through hydrogen bonding and therefore a poorer carbanion trap. The fact that TBA addition to the brom-

ide (entry 3, Table V) resulted in less than 1% hydrocarbon formation indicates that HME is not very important in the case of the bromides; however, in the case of the iodide, 22% of the uncyclized hydrocarbon was formed (entry 5) indicating that HME is much more important in the mechanistic pathway describing the iodide reaction than the bromide reaction.

In addition, when a smaller amount of radical trap DCPH was used (entry 2) in the reaction of Me_3SnNa with **9**, more hydrocarbons **10** and **11** were formed than when more DCPH was used (entry 3). Again, this result indicates that radical escape from the solvent cage in the less viscous solvent (THF + 1 molar equiv of DCPH) is easier compared to the more viscous solvent (THF + 10 molar equiv of DCPH). Moreover, when the reactions were carried out at lower temperatures (−23 and −78 °C), the yield of substitution product was increased dramatically. Lowering the reaction temperature should increase the viscosity of the solvent and hence the amount of uncyclized substitution product (entries 7–12). As suggested earlier, these results can also be due to a change in $\Delta(\Delta G^{\ddagger})$ for the three reaction pathways (S_N2, HME, and ET) in Scheme III. Especially, the HME pathway becomes less favorable at lower temperature as evidenced by the small amount of **10** and **11** formed by carbanion trapping (entries 9 and 12).

Studies with Dihaloalkane. Next, we examined the reaction of **1** with the *exo,cis*-1,2-bis(halomethyl)bicyclo-[2.2.1]heptanes (**18** and **19**), and the results are shown in Table VII. Entry 1 shows that the reaction of *1* with dibromide **18** produces a substantial amount of disubstituted product **23** (69.5%), monosubstituted hydrocarbon **22** (7.5%), and cyclized hydrocarbon **21** (19.7%) in the absence of any additive. It is clear that both **21** and **22** can be formed by both ET and HME, and thus S_N2 can be completely excluded as a pathway for **21** and for the hydrocarbon portion of **22**. The method of evaluation used earlier to distinguish ET from HME, i.e., DCPH trap for radicals and carbanions and TBA trap just for carbanions, was used in this study as well. When DCPH was added (entry 2), the amount of disubstituted product **23** was substantially decreased from 69.5% to 36.7% and the amount of **22** increased from 7.5% to 31%. In order to determine the involvement of a carbanion intermediate, TBA was used resulting in an increase in the amount of **22** formed (7.5–20.2%) and a decrease in the amount of **21** and **23**. Entry 4 shows that **24** is an intermediate in this reaction and the precursor to **22**. These results clearly indicate that both ET and HME are involved in this reaction to a similar extent and the reaction pathways are represented by Scheme V.

When the reaction of **1** with **19** (the corresponding iodide) was studied, substantially different results were obtained. The major product was the cyclized hydrocarbon **21** which can be formed by both ET and HME pathways (Scheme V). Entry 6 shows that DCPH is an effective trap by decreasing the amount of **21** formed from 89.8 to 76.4% and increasing the amount of **20** formed from <1 to 6.3%. Since TBA addition (entry 7) shows no trapping, one can assume that the DCPH result is due to trapping just the radical; therefore, ET represents at least part of what is happening in this reaction.

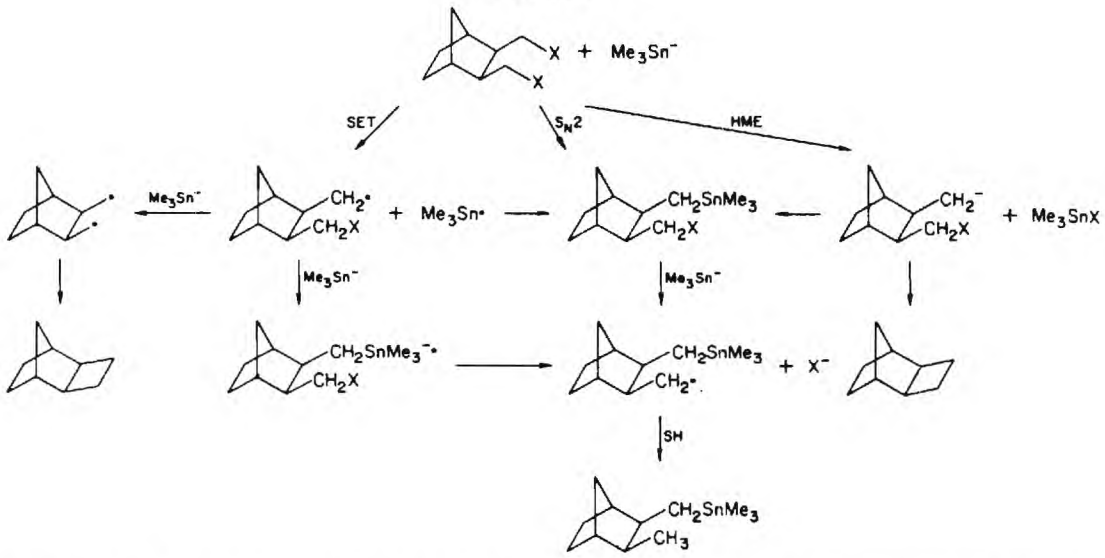
Since it is not possible to form the major product **21** by an S_N2 process, this leaves only HME as another possible reaction pathway. Since TBA was effective in trapping the carbanion precursor to **21** in the reaction with the bromide (entry 3), this does not mean that it would be effective in trapping the carbanion precursor to **21** pro-

Table VII. Reaction of *exo,cis*-1,2-Bis(halomethyl)bicyclo[2.2.1]heptane (18 and 19) with Me_3SnNa (1) in THF[a]

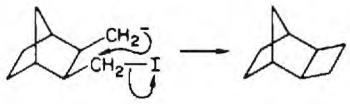
entry	X	temp, °C	additive,[b] molar equiv	20	21	22	23	24	
1	Br (18)	0	none	<1	19.7	7.5	69.5	0	0
2	Br	0	DCPH, 4	2.0	15.9	31.0	36.7	0	0
3	Br	0	TBA, 10	<1	8.9	20.2	59.2	0	0
4	Br	−78	none	0	3.4	0	28.6	30	30
5	I (19)	0	0	<1	89.8	<1	1.0	0	0
6	I	0	DCPH, 4	7.3	76.4	2.0	<1	0	0
7	I	0	TBA, 10	1.5	90.6	<1	<1	0	0
8	I	−78	none	0	85.0	<1	3.2	0	0

[a] Reactions were conducted by using 0.05 M concentrations of halide and 0.15 M concentrations of Me_3SnNa for 30 min. [b] Based on halide.

Scheme V



duced from the iodide. This is so because iodide is a much better leaving group than bromide, and it is reasonable that the rate of intramolecular attack of the carbanion at the backside of the CH_2–I group is considerably faster than bimolecular abstraction of proton from TBA by the intermediate carbanion, and therefore in the former case TBA has less chance of trapping the carbanion intermediate (eq 5).



(5)

Conclusions

The reaction of a series of primary alkyl bromides with Me_3SnNa was examined. The results are inconsistent with previous reports[10,11] that radicals are not involved. By lowering the viscosity of the solvent, by lowering the cation coordinating ability of the solvent, or by running the reactions in the presence of a radical trap, it has been established that radical intermediates are involved in this type of reaction at least for the systems studied. Furthermore, the reaction of a primary alkyl iodide containing a cyclizable radical probe with Me_3SnNa was also examined, and it was found that this reaction does not react exclusively via S_N2 and HME pathways as previously reported but also reacts via an ET pathway to a significant extent.

Experimental Section

General Procedures and Materials. Solvent grade pentane was stirred over concentrated H_2SO_4, washed with water, dried over $MgSO_4$, and distilled from $NaAlH_4$ under nitrogen. Reagent grade diethyl ether (Fisher) and reagent grade THF were distilled under nitrogen from deep purple solutions of sodium benzophenone ketyl.

Samples of dicyclohexylphosphine (DCPH, bp 68–70 °C (0.05 mm Hg)), 1-bromobutane (bp 101–103 °C, CaH_2), 1-bromo-2-methylpropane (bp 90–92 °C, CaH_2), 2-ethylhexyl bromide (bp 75–77 °C (16 mmHg), CaH_2), and methyl acrylate were purchased from Aldrich and purified by distillation. Reagent grade acetone (Fisher), pyridine (Fisher), tosyl chloride (Aldrich), paraformaldehyde (Aldrich), dicyclopentadiene (Aldrich), 5-hexen-1-ol (Aldrich), lithium bromide (Aldrich), and sodium iodide (Fisher) were used as received. Resublimed magnesium chips, anhydrous metal salts, sodium dispersion, di-*tert*-butylnitroxyl radical, and hexamethylditin (bp 73–74 °C at 16 mmHg) were purchased from Alfa.

Gas chromatographic analyses were conducted on a Varian 3700 (FID) instrument coupled to a Varian CDS III electronic integrator using a DB-1 capillary column. Quantitative GLC analyses were obtained with the use of response factors, corrected peak areas, and using internal standards. Proton NMR spectra were recorded on a Varian T60 spectrometer. Infrared spectra were recorded on a Perkin-Elmer Model 621 spectrophotometer. Mass spectra were obtained by using a Varian MAT 1125 instrument, and carbon–hydrogen microanalyses were conducted by Atlanta Microlabs, Inc., of Atlanta, GA. Viscosities were determined by using an Ostwald viscosimeter.

Preparation of (Trimethylstannyl)sodium (1). Following the literature procedure,[11] **1** was prepared via the reaction of hexamethylditin with sodium dispersion at 0 °C in THF and analyzed by the reaction of an aliquot with *n*-BuBr, followed by the GLC analysis for *n*-$BuSnMe_3$.

Preparation of 6-Bromo-1-hexene (7). The 6-tosyl-1-hexene prepared from the corresponding alcohol (pyridine, TsCl, 0 °C) was converted to the corresponding bromide (acetone, LiBr (fivefold excess), reflux, 4 h) in 82% yield; bp 73–75 °C (73 mmHg).

Preparation of *endo*-5-(2-Haloethyl)-2-norbornene (9 and 10). By use of published procedure,[15] **9** and **10** were obtained. For X = Br: bp 71–73 °C (2.5 mmHg); ^{1}H NMR δ 0.5–0.6 (1 H, m), 2.6–2.8 (2 H, m), 3.4 (2 H, t, J = 7 Hz), 5.8–6.2 (2 H, m). For X = I: bp 83–84 °C (2.5 mmHg); ^{1}H NMR δ 0.5–0.6 (1 H, m), 1.0–2.2 (5 H, m), 2.6–2.8 (2 H, m), 3.2 (2 H, t, J = 7 Hz), 5.8–6.2 (2 H, m).

Preparation of *exo,cis*-1,2-Bis(halomethyl)bicyclo[2.2.1]heptane (18 and 19). By use of a published procedure,[16] **18** and **19** were obtained. For X = Br: mp 44.5–45 °C (recrystallized from MeOH); ^{1}H NMR δ 1.08–1.13 (1 H, m), 1.26–1.31 (2 H, m), 1.40–1.44 (1 H, m), 1.57–1.61 (2 H, m), 2.15–2.19 (2 H, m), 2.41–2.42 (2 H, m), 3.16–3.23 (2 H, m), 3.53–3.58 (2 H, m). For X = I: mp 80–80.5 °C (recrystallized from MeOH; lit.[16] mp 80 °C); ^{1}H NMR δ 1.05–1.10 (1 H, m), 1.23–1.31 (2 H, m), 1.38–1.44 (1 H, m), 1.55–1.63 (2 H, m), 2.11–2.21 (2 H, m), 2.47–2.49 (2 H, m), 2.93–3.02 (2 H, m), 3.37–3.44 (2 H, m).

General Procedure for Reactions of Primary Alkyl Halides with Me_3SnNa (1). Reaction of Me_3SnNa with *n*-BuBr in the Presence of *p*-Dinitrobenzene (2). To 0.5 mL of a 0.42 M solution of bromide containing 9.7 mg (0.058 mmol) of **2** in THF under N_2 was added 1.2 mL of a 0.35 M solution of **1** in THF at 0 °C. After a certain time period, with stirring, the reaction mixture was quenched with water and analyzed by GLC.

Reaction of Me_3SnNa (1) with 6-Bromo-1-hexene (7) in the Presence of TBA–Solvent (THF–Et_2O (1:1)). To a solution of the bromide (0.28 mmol) and TBA (2.8 mmol) in 2.6 mL of

(15) Ashby, E. C.; Pham, T. N., *Tetrahedron Lett.* **1984**, *25*, 4333.
(16) Alder, K.; Monch, J.; Wirtz, H. *Liebig Ann. Chem.* **1959**, *627*, 47.

mixed solvent (0.5 mL of dry THF and 2.1 mL of dry ether) under N_2 was added 1.6 mL of a 0.35 M solution of **1** in THF at 0 °C. After a certain time period, with stirring, the reaction mixture was quenched with water and analyzed by GLC. Both uncyclized and cyclized substitution products were confirmed by GC–MS and NMR spectrometry.

Reaction of Me_3SnNa (1) with *endo*-5-(2-Bromoethyl)-2-norbornene (8) in the Presence of DCPH–Solvent (THF–Pentane (1:1)). To a solution of the bromide (0.05 mmol) and DCPH (0.05 mmol) in 0.71 mL of mixed solvent (0.21 mL of dry THF and 0.50 mL of dry pentane) under N_2 was added 0.29 mL of a 0.35 M solution of **1** in THF at 0 °C. After 15 min, with stirring, the reaction mixture was quenched with water and analyzed by GLC. All products were confirmed by GC–MS and NMR spectroscopies. *endo*-5-(2-(Trimethylstannyl)ethyl)-2-norbornene: ^{1}H NMR δ 0.05 (9 H, s, J(SnCH) = 48 Hz), 0.44–1.50 (7 H, m), 1.66–2.04 (2 H, m), 2.64–2.89 (2 H, m), 5.8–6.2 (2 H, m). Anal. Calcd: C, 50.56; H, 7.79. Found: C, 50.68; H, 7.80. *endo*-5-Ethyl-2-norbornene (**10**): ^{1}H NMR δ 0.5–0.6 (1 H, m), 0.8–0.9 (3 H, d, J = 4 Hz), 1.0–1.4 (4 H, m), 1.65–1.9 (2 H, m), 2.6–2.8 (2 H, m), 5.8–6.2 (2 H, m). Tricyclo[4.2.1.$0^{3,7}$]nonane (**11**): ^{1}H NMR δ 0.70 (1 H, m), 0.87 (1 H, m), 1.15–1.9 (12 H, m); mp 99–100 °C (lit.[17] mp 98–99 °C).

Control Experiments: Reaction of TBA and DCPH with Halides. In a typical experiment, 1.5 mmol of an additive under N_2 was added to 0.15 mmol of halide in 0.5 mL of dry THF at 0 °C. After 1 h the solution was analyzed by GLC.

Acknowledgment. We are indebted to the National Science Foundation Grant No. CHE 8403024 for support of this work.

Registry No. **1**, 16643-09-7; **4**, 109-65-9; **6**, 18908-66-2; **7**, 2695-47-8; **8**, 94417-50-2; **9**, 94417-49-9; **10**, 32166-37-3; **11**, 1521-75-1; **18**, 97232-56-9; **19**, 85807-80-3; 5-hexen-1-ol, 821-41-0; *endo*-5-(2-trimethylstannylethyl)-2-norbornene, 97150-43-1.

(17) Nickson, A.; Kwasnik, H. R.; Mathew, C. J.; Swartz, T. D.; Williams, R. O.; Digiorgo, J. B. *J. Org. Chem.* **1978**, *43*, 3904.

Single Electron Transfer in the Reaction of Enolates with Alkyl Halides

E. C. Ashby* and J. N. Argyropoulos

School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

Received January 9, 1985

Single electron transfer (SET) in the reaction of a model system consisting of lithiopropiophenone with primary neopentyl type alkyl halides and tosylate was investigated by (1) the use of an appropriate cyclizable alkyl radical probe, (2) observing the effect of varying the leaving group on reaction rate and product distribution, (3) studying the effect of light, di-*tert*-butyl nitroxyl radical, and *p*-dinitrobenzene on the rate of reaction, (4) observing the consequence of varying solvent composition on both the reaction rate and product distribution, and (5) studying the effects of the radical traps, dicyclohexylphosphine and 1,4-cyclohexadiene, on product composition. The results of these studies indicate that single electron transfer is the major reaction pathway involved in the reaction of the enolate with the alkyl iodide in HMPA and that the corresponding bromide and tosylate react by an S_N2 process.

The reaction of an enolate anion with an alkyl substrate (halide or tosylate) is well-recognized as an important synthetic reaction in organic chemistry.[1] Although the mechanism of this reaction is generally believed to proceed

0022-3263/85/1950-3274$01.50/0

Table I. Effect of Leaving Group on the Reaction of Lithiopropiophenone with 1-Halo-2,2-dimethyl-5-hexenes 12–14 in HMPA[a]

expt		time, h	unreacted starting material	% yield 1	2	3	4	5	6	7
1	X = I	10	48	0[c]	tr[b,d]	tr	42	8.2	0.74	0
2	X = I	60	8.0	0	1.0	0.88	66	11	1.0	0
3	X = Br	60	76	0	0	0	20	0.70	0	0
4	X = Br	170	57	0	0	0	30	0.73	0	0
5	X = OTs	60	98	0	0	0	4.4	0	0	0

[a] All reactions were carried out at a reactant ratio of 1:2 (alkyl substrate:lithiopropiophenone) and 0.10 M in alkyl substrate at room temperature. [b] 0.10 < % yield < 0.50. [c] % yield < 0.10. [d] tr = trace.

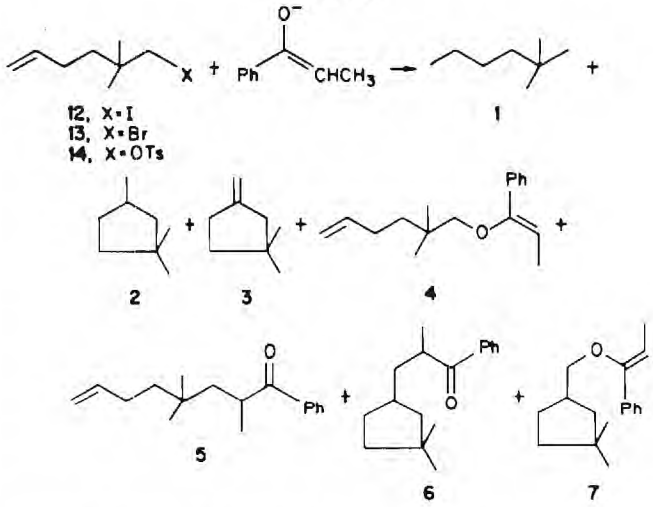
by an S_N2 process, Kornblum has demonstrated that for reactions involving *p*-nitrobenzyl chloride a $S_{RN}1$ type radical–radical anion chain mechanism is involved.[2] Russell has also shown that the $S_{RN}1$ mechanism is involved in the reaction of $XCMe_2NO_2$ (X = Cl, NO_2, or *p*-$MeC_6H_4SO_2$) with lithium enolates.[3] Bunnett later proposed this mechanistic pathway for aromatic substitution reactions.[4] Furthermore, Zook suggested that typical aliphatic halides could be reacting with enolate anions by an electron-transfer process when he observed small quantities of alkanes in his reaction mixtures.[5]

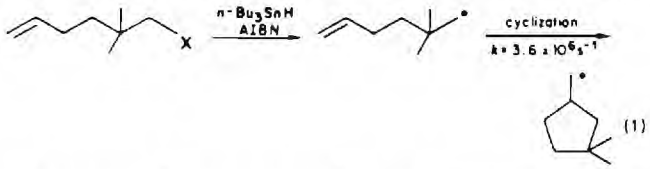
The ability of an enolate anion to serve as a one electron donor toward a variety of other organic substrates is well documented. Examples of such substrates include *p*-dinitrobenzene,[6] *p*-nitrobenzoyl esters,[7] and diaryl ketones.[6,8] With this background and our results with reactions of metal hydrides,[9] alkoxides,[10] amides,[11] and cuprates[12] with cyclizable alkyl halide probes, we chose to embark on a detailed mechanistic study involving lithiopropiophenone with cyclizable alkyl halide and tosylate probes.[13]

The radical probe chosen for the present study was 2,2-dimethyl-1-iodo-5-hexene and its bromo and tosylate derivatives. We have successfully used this probe in a number of investigations[9–12] including the mechanistic study of Grignard reagent addition to aromatic ketones.[14] More recently, Beckwith[15] reported that the 2,2-dimethyl-5-hexen-1-yl radical undergoes cyclization at a rate about 15 times faster than that of the parent 5-hexen-1-yl radical[16] (eq 1). Furthermore, the 1-halo-2,2-dimethyl-5-hexenes and the corresponding tosylate cannot undergo elimination when allowed to react with bases such as enolates.[5] If single electron transfer (SET) is taking place in the reaction of lithiopropiophenone with the neopentyl type probes, the radical recombination step of the resulting bulky neopentyl type radical should be slower than that of the 5-hexen-1-yl radical and hence there should be a better opportunity for observing cyclization of the probe. In addition, the steric hindrance of the alkyl substrate should raise the activation energy for the S_N2 process more than that for an SET process. Thus for a sterically hindered system, it is possible that an SET pathway is preferred because the S_N2 pathway is discouraged.[17] For the above reasons, 2,2-dimethyl-1-iodo-5-hexene and its derivatives seemed to be ideal candidates to study the degree that an SET process is possible in the reaction of a lithium enolate with a primary alkyl halide or tosylate.

In the present study, we report the results of reacting a simple enolate, lithiopropiophenone, with primary neopentyl type alkyl halide and tosylate probes in various solvents including HMPA. No systematic studies of simple

Scheme I





(1)

(1) (a) House, H. O. "Modern Synthetic Reactions", 2nd ed.; Benjamin: Menlo Park, CA, 1972; Chapter 9. (b) Caine, D. S. In "Carbon–Carbon Bond Formation"; Augustine, R. L. Ed.; Marcel Dekker, Inc.: New York, 1979; Vol. 1, Chapter 2. (c) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737.

(2) (a) Kornblum, N.; Michel, R. E.; Kerber, R. C. *J. Am. Chem. Soc.* **1966**, *88*, 5660. (b) Kornblum, N.; Michel, R. E.; Kerber, R. C. *Ibid.* **1966**, *88*, 5662. (c) Kornblum, N.; Boyd, S. D.; Stuchal, F. W. *Ibid.* **1970**, *92*, 5783. (d) Kornblum, N. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 734.

(3) (a) Russell, G. A.; Danen, W. C. *J. Am. Chem. Soc.* **1966**, *88*, 5663. (b) Russell, G. A.; Jawdosiuk, M.; Ros, F. *Ibid.* **1979**, *101*, 3378. (c) Russell, G. A.; Mudryk, B.; Jawdosiuk, M. *Ibid.* **1981**, *103*, 4610.

(4) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413.

(5) Zook, H. D.; Kelly, W. L.; Posey, I. Y. *J. Org. Chem.* **1968**, *33*, 3477.

(6) Russell, G. A.; Janzen, E. G.; Strom, E. T. *J. Am. Chem. Soc.* **1964**, *86*, 1807.

(7) Ashby, E. C.; Park, W. S. *Tetrahedron Lett.* **1983**, *24*, 1667.

(8) Ashby, E. C.; Argyropoulos, J. N.; Meyer, G. R.; Goel, A. B. *J. Am. Chem. Soc.* **1982**, *104*, 6788.

(9) (a) Ashby, E. C.; DePriest, R. N.; Goel, A. B. *Tetrahedron Lett.* **1981**, *22*, 1763. (b) Ashby, E. C.; DePriest, R. N.; Pham, T. N. *Tetrahedron Lett.* **1983**, *24*, 2825. (c) Ashby, E. C.; DePriest, R. N.; Goel, A. B.; Wenderoth, B.; Pham, T. N. *J. Org. Chem.* **1984**, *49*, 3545.

(10) Ashby, E. C.; Bae, D. H.; Park, W. S.; DePriest, R. N.; Su, W. Y. *Tetrahedron Lett.* **1984**, *25*, 5107.

(11) Ashby, E. C.; Goel, A. B.; DePriest, R. N. *J. Org. Chem.* **1981**, *46*, 2429.

(12) Ashby, E. C.; DePriest, R. N.; Tuncay, A.; Srivastava, S. *Tetrahedron Lett.* **1982**, *23*, 5251.

(13) Ashby, E. C.; Argyropoulos, J. N. *Tetrahedron Lett.* **1984**, *25*, 7.

(14) Ashby, E. C. *Pure Appl. Chem.* **1980**, *52*, 545.

(15) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, *36*, 545.

(16) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317.

(17) Kochi, J. K. "Organometallic Mechanisms and Catalysis"; Academic Press: New York, 1978; pp 532–535.

Table II. Effect of Light, Absence of Light, and Radical Scavenger on the Reaction of Lithiopropiophenone with 2,2-Dimethyl-1-iodo-5-hexene (12) in HMPA[a]

			% yield						
expt	conditions	time, h	12	1	2	3	4	5	6
1	light	10	48	0	tr[b]	tr	42	8.2	0.74
6	no light	10	47	0	tr	tr	44	7.4	0.55
7	0.10 equiv of $(t\text{-Bu})_2NO$	10	48	0	tr	tr	44	7.3	tr

[a] All reactions were carried out at a reactant ratio of 1:2 (alkyl iodide:lithiopropiophenone) and 0.10 M in alkyl iodide at room temperature. [b] tr = trace.

enolates in HMPA are known to our knowledge.[1c] Furthermore, previous attempts to utilize neopentyl type alkyl halides as alkylating agents toward enolates have led to poor yields of alkylation product.[18] In order to determine the degree to which an SET pathway participates in this reaction, we examined the effects of radical scavengers, radical traps, solvent, and leaving group on both reaction rate and product distribution.

Results and Discussion

The reactivity and product orientation of enolate anions in their reactions with alkyl halides and tosylates have been the subject of considerable interest.[1c,19] In this connection we have studied the reaction of lithiopropiophenone with 2,2-dimethyl-1-iodo-5-hexene (**12**) and its bromo (**13**) and tosylate (**14**) derivatives. Scheme I shows the products **1**–**7** which can be formed in this reaction. The straight-chain O-alkylation product, compound **4**, and C-alkylation product, compound **5**, can arise from either an S_N2 or SET pathway. The cyclic alkylation products, compounds **6** and **7**, as well as the hydrocarbon products, compounds **1**–**3**, can only arise via a radical pathway. The effects of a variety of factors on this product distribution will now be examined in detail.

Effect of Leaving Group. The results of the reaction of lithiopropiophenone with 2,2-dimethyl-1-iodo-5-hexene and its bromo and tosylate derivatives are reported in Table I. The nature of the leaving group has a pronounced effect on both product distribution and rate of reaction.

In all of the reactions (experiments 1–5), the major product is the straight-chain O-alkylation compound. This is not surprising since the O-terminus of the enolate anion lacks the encumbrance due to the lithium cation in a solvent such as hexamethylphosphoramide (HMPA).[1c] Furthermore, O-alkylation is favored in the order RI < RBr < ROTs as is predicted by Pearson's theory of hard and soft acids and bases (HSAB theory).[20] Since the O-terminus is "harder" than the C-terminus, O-alkylation is most favored by the "hardest" leaving group, OTs > Br > I. The O/C ratio at the half-life of the alkyl iodide reaction, experiment 1, is 4.7. On the other hand, the O/C ratio at the half-life of the alkyl bromide reaction, experiment 4, is 41. The reason for the large difference in the O/C ratio of the alkyl iodide and bromide cannot be completely rationalized by HSAB theory; indeed, the two alkyl halides may be reacting by different pathways. It is known that radical reactions give lower O/C ratios than that observed for an S_N2 process.[2]

Further evidence that 2,2-dimethyl-1-iodo-5-hexene may be reacting by a different pathway from its bromo and tosylate derivatives is indicated by the formation of small amounts of hydrocarbons **2** and **3** as well as cyclized C-alkylation product, compound **6**. The hydrocarbons can arise from disproportionation of the cyclized radical (radical **2**-a in Scheme III). The cyclized C-alkylation product (**6**), which represents 8.3% of the total C-alkylation products (**5**, **6**), can also arise from radical **2**-a in Scheme III by the coupling reaction of the cyclized radical with the enolate radical. Interestingly, no cyclized O-alkylation product, compound **7**, was observed. None of the radical byproducts present in the alkyl iodide reaction, experiments 1 and 2, could be detected in the alkyl bromide and tosylate reactions, experiments 3–5, suggesting that the alkyl iodide may be reacting by a different pathway from the alkyl bromide and tosylate. In fact the only product formed in significant amount in the reaction of lithiopropiophenone with the alkyl bromide and tosylate is the O-alkylation product, compound **4**.

The reactivity of the cyclizable alkyl halide and tosylate probes was found to strongly rely on the nature of the leaving group. As seen from Table I, the alkyl iodide reaction has an approximate half-life of 10 h. The alkyl bromide reaction is not 50% complete even after 170 h, whereas the tosylate is virtually unreactive. The lack of reactivity for the tosylate appears surprising when one notes that alkyl tosylates normally exhibit reactivity that is similar to that of the corresponding alkyl iodides in their reactions with enolate anions.[21] In fact, Mosher reports that neopentyl tosylate undergoes normal nucleophilic displacements in HMPA solvent with a variety of nucleophiles, except enolates.[22] Hence, the ordering of leaving group ability in the S_N2 process I ~ OTs > Br apparently is not obeyed in the reaction of lithiopropiophenone with the neopentyl type probes in HMPA.

An alternate explanation based on the reduction potentials of alkyl substrates can be given. Electrochemical data concerning the reduction potentials of alkyl halides and tosylates demonstrate that alkyl iodides have lower reduction potentials than alkyl bromides, whereas in tosylates the C–O bond is not electrochemically cleaved.[23] Lipshutz et al. have recently reported electrochemical data that are "in line with the anticipated propensity of an iodide to undergo a one-electron reduction to afford an intermediate radical" but for tosylates "the S–O bond is ultimately broken, suggesting that in their substitution reactions, tosylates participate in a direct two-electron process." Hence, for an SET process, the order of reactivity based on leaving group is R–I > R–Br ≫ R–OTs which is consistent with our observations (Table I).

Effect of Light and Radical Scavenger. The possibility that the O- and C-alkylation products are arising from an $S_{RN}1$ pathway, as illustrated in Scheme II, is

(18) (a) LeNoble, W. J.; Morris, H. F. *J. Org. Chem.* **1969**, *34*, 1969. (b) Zook, H. D.; Rellahan, W. L. *J. Am. Chem. Soc.* **1957**, *79*, 881.
(19) Jackman, L. M.; Lange, B. C. *J. Am. Chem. Soc.* **1981**, *103*, 4494.
(20) Pearson, R. G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, *89*, 1827.
(21) (a) House, H. O.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 2502. (b) Conia, J. M. *Bull. Soc. Chem. Fr.* **1950**, 533.
(22) Stephenson, B.; Solladie, G.; Mosher, H. S. *J. Am. Chem. Soc.* **1972**, *94*, 4184.
(23) (a) Lipshutz, B. H.; Wilhelm, R. S.; Nugent, S. T.; Little, R. D.; Baizen, M. M. *J. Org. Chem.* **1983**, *48*, 3306. (b) Mbarak, M. S.; Peters, D. G. *J. Org. Chem.* **1982**, *47*, 3397. (c) Mann, C. K.; Barnes, K. K. "Electrochemical Reactions in Nonaqueous Systems"; Marcel Dekker: New York, 1970; pp 201–205.

Scheme II

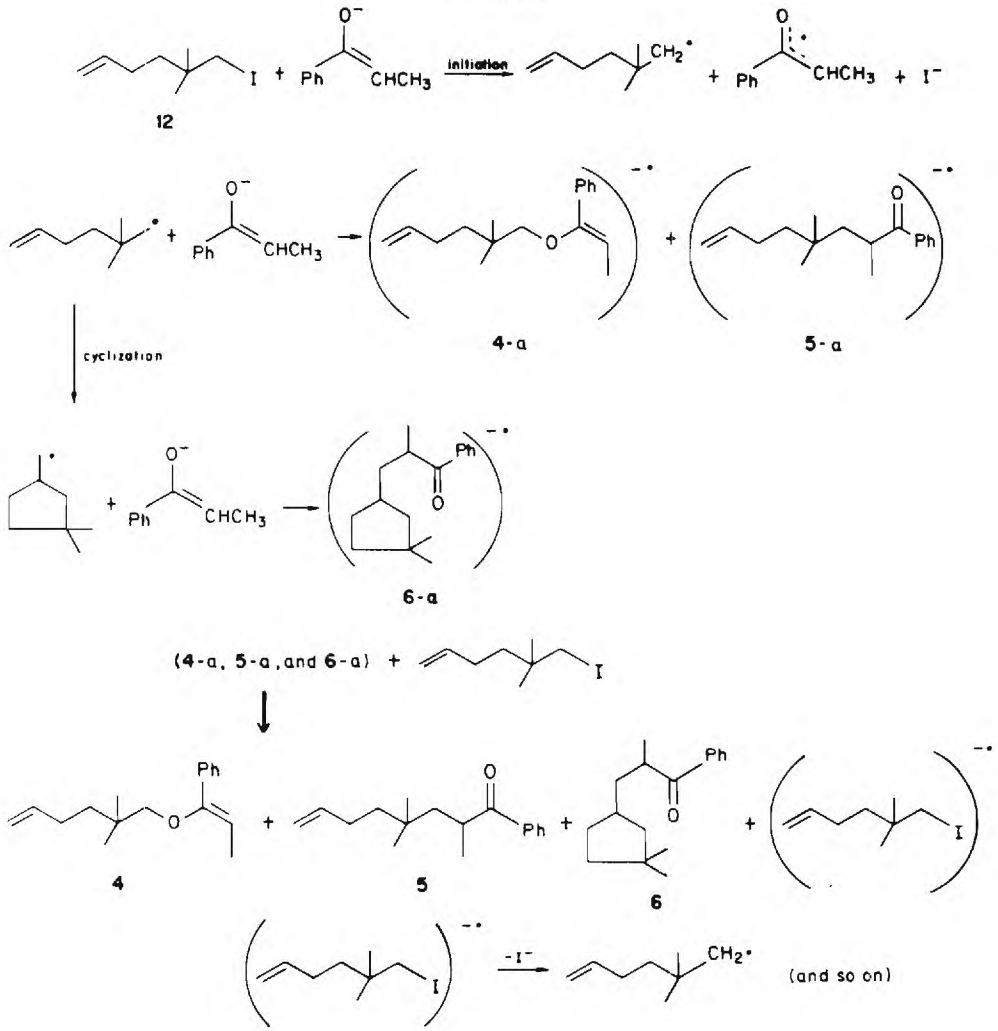


Table III. Effect of Solvent on the Reaction of Lithiopropiophenone with 2,2-Dimethyl-1-iodo-5-hexene (12)[a]

			% yield							4 + 5
expt	solvent	time, h	12	1	2	3	4	5	6	1 + 2 + 3 + 6
2	HMPA	60	8.0	0	1.0	0.88	66	11	1.0	26.7[c]
8	20% THF in HMPA[b]	60	25	0	2.2	2.0	60	12	1.2	13.3
9	20% PhH in HMPA[b]	60	22	0	3.0	2.9	49	10	2.1	7.4
10	15% HMPA in THF[b]	60	98	0	0	0	0	0	0	
11	THF	60	99	0	0	0	0	0	0	

[a] All reactions were carried out at a reactant ratio of 1:2 (alkyl iodide:lithiopropiophenone) and 0.10 M in alkyl iodide at room temperature. [b] Percentage based on volume. [c] ±10%.

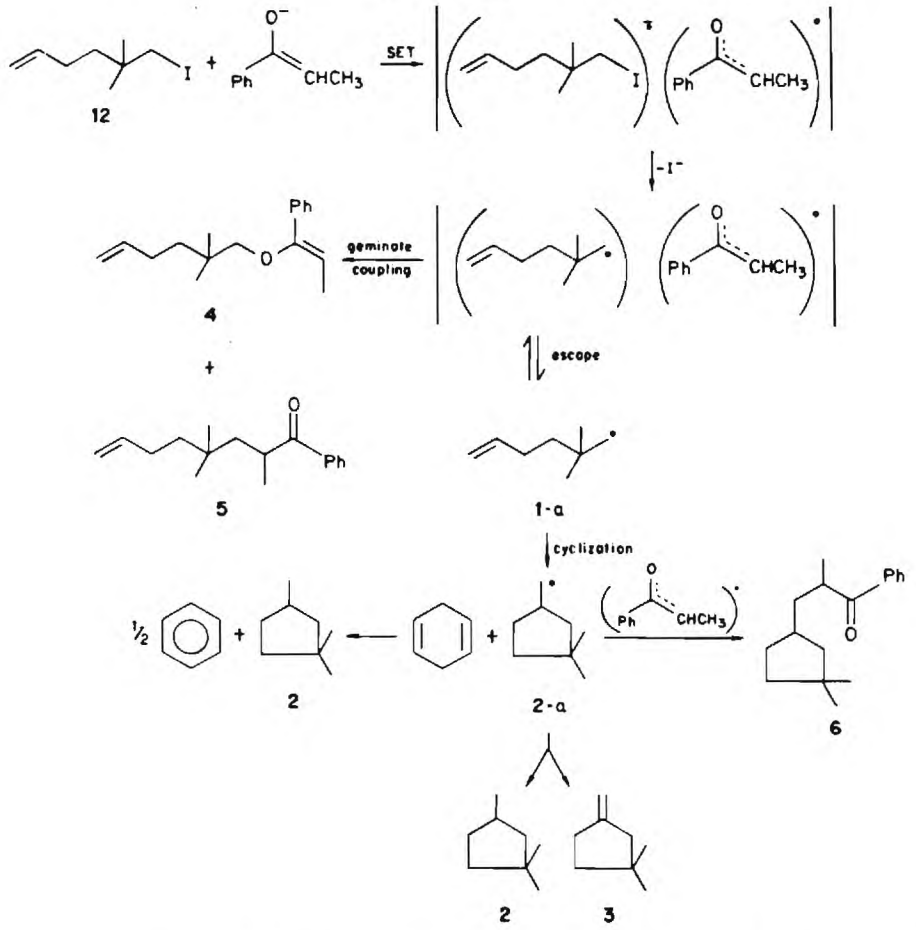
reasonable for the formation of the substitution products, compounds 4–6.[2-4]

Reactions were carried out under ambient fluorescent light, absence of light, and with an efficient free radical scavenger, di-*tert*-butyl nitroxyl radical, in order to determine what effect these factors have on both the reaction rate and product distribution. The results of these experiments are shown in Table II. The reaction of lithiopropiophenone with 2,2-dimethyl-1-iodo-5-hexene was found to be insensitive to the factors that normally influence the $S_{RN}1$ pathway. Furthermore, the product distributions in going from experiment 1 to experiments 6 and 7 in Table II remain fairly constant and, hence, further suggest that the $S_{RN}1$ pathway is not operating in this reaction.

Effect of Solvent. The reaction of lithiopropiophenone with 2,2-dimethyl-1-iodo-5-hexene showed a strong dependence on the nature of the solvent. In HMPA the reaction is essentially complete in 60 h; conversely, the reaction does not proceed at all in THF (experiment 11, Table III). These results are not surprising when one considers that lithium enolates are more reactive in a class C solvent such as HMPA than in a class B solvent like THF.[1] House[24] and then Jackman[19] showed that the addition of 4 equiv of HMPA to a solution of a lithium enolate in a class B solvent causes a significant upfield shift in the ^{13}C spectrum of the carbon bearing the oxygen. This observation is indicative of selective solvation of the lithium cation. The further addition of 1 equiv of HMPA causes no additional upfield shift of the carbon. Hence, the addition of 4 equiv of HMPA "converts lithium enolates into highly reactive solvent-separated ion pairs", and if additional quantities of HMPA are employed, "enolate

(24) House, H. O.; Prabhee, A. V.; Phillips, W. V. *J. Org. Chem.* **1976**, *41*, 1209.

Scheme III



reactivity is not influenced significantly".[1b] Our attempt to react lithiopropiophenone with the alkyl iodide probe in THF utilizing 4 equiv of HMPA led to no reaction (experiment 10). Even when 8 equiv of HMPA were used, no reaction occurred. Furthermore, the addition of even a small amount of THF or benzene to the HMPA solution of lithiopropiophenone, experiments 8 and 9, had a retarding effect on the rate of reaction of the lithium enolate with the alkyl iodide. Clearly, in this reaction, HMPA must play a greater role than just complexing the lithium cation.

Recently, Lipshutz[23] showed that solvent plays a pivotal role in determining the reduction potentials of alkyl halides, with a significant increase in the reduction potential of the alkyl halide in going from THF to CH_3CN to DMF. The rate of reaction of lithiopropiophenone with the alkyl iodide probe as shown in Scheme III depends on the extent of single electron transfer which in turn is governed by the reduction potential of the alkyl iodide. Hence, as more and more THF is added to the solution of the lithium enolate and alkyl iodide in HMPA, the reduction potential of the iodide becomes a more negative value until at some point the reduction potential is too unfavorable for electron transfer to occur and no reaction is observed.

As shown in Scheme III, the amount of cyclized products, compounds **2**, **3**, and **6**, depends on the rate of cyclization of radical **1-a** vs. geminate coupling. Since $k_{(cyclization)} = 3.6 \times 10^6\ s^{-1}$ for radical **1-a**,[15] whereas rate constants for geminate coupling range from 10^8–$10^{10}\ M^{-1}\ s^{-1}$,[25] it is not surprising that the straight-chain alkylation products predominate. Furthermore, if Scheme III describes the mechanism of reaction of lithiopropiophenone with 2,2-dimethyl-1-iodo-5-hexene, then solvent viscosity should have an effect on the ratio of straight-chain alkylation products to cyclic products since the relative rates of coupling within the solvent cage and diffusion from the cage are viscosity dependent.[25,26] Koenig[27] has used a simple diffusion model to develop a relationship between viscosity and the yield of geminate coupled product (eq 2). Hence, as the viscosity of the solvent (η) decreases,

$$1/\phi - 1 = a + b/\eta^{1/2} \qquad (2)$$

the yield of product formed in the cage (ϕ) should also decrease. As shown in Table III, the ratio of compounds **4** and **5** (the cage combination products) to compounds **2**, **3**, and **6** (the cyclic products formed outside the cage) is dependent on the solvent viscosity. As the solvent viscosity decreases in going from HMPA to 20% THF or benzene in HMPA ($\eta^{20\,°C}_{THF} = 0.55$, $\eta^{20\,°C}_{\phi H} = 0.6487$, $\eta^{20\,°C}_{HMPA} = 3.47$),[28] the ratio of (**4** + **5**)/(**2** + **3** + **6**) decreases. The viscosity dependence lends strong support to the cage process in Scheme III.

Effect of Hydrogen Atom Donors. The trapping of free radicals by hydrogen atom donors is an important method for establishing the intermediacy of free radicals.[25] In particular two hydrogen atom donors that have found

(25) Kochi, J. K., Ed. "Free Radicals"; Wiley and Sons: New York, 1973; Vol. 1, Chapters 2, 4, and 7.

(26) Wursthorn, K. R.; Kuivila, H. G.; Smith, G. F. *J. Am. Chem. Soc.* **1978**, *100*, 2779.

(27) Koenig, T. *J. Am. Chem. Soc.* **1969**, *91*, 2558.

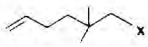
(28) Riddick, J. A.; Bunger, W. B. "Organic Solvents", 3rd ed.; Wiley and Sons: New York, 1970; Chapter 3.

Table IV. Effect of 1,4-Cyclohexadiene on the Reaction of Lithiopropiophenone with 2,2-Dimethyl-1-iodo-5-hexene (12) in HMPA[a]

			% yield							
expt	 [b]	time, h	12	1	2	3	4	5	6	
2	0	60	8.0	0	1.0	0.88	66	11	1.0	
12	5	60	12	0	11	0	54	9.1	0.50	5.8[b]
13	15	60	18	1.0	28	0	36	6.1	tr[d]	16
14[c]	15	70	99	0	0	0				

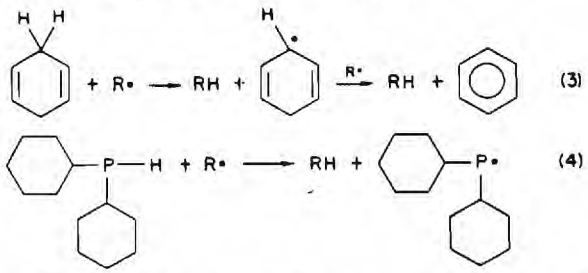
[a] All reactions were carried out at a reactant ratio of 1:2 (alkyl iodide:lithiopropiophenone) and 0.10 M in alkyl iodide at room temperature unless otherwise stated. [b] Equivalents based on alkyl iodide. [c] No lithiopropiophenone (control experiment). [d] tr = trace.

Table V. Effect of Dicyclohexylphosphine on the Reaction of Lithiopropiophenone with 1-Halo-2,2-dimethyl-5-hexenes 12 and 13 in HMPA[a]

				% yield					
expt		additives	time, h	unreacted starting material	1	2	3	4	5	6
1	X = I	none	10	48	0	tr[c]	tr	42	8.2	0.74
15	X = I	1.0 equiv of DCPH[b]	1	49	0.84	44	1.2	2.2	tr	2.1
16	X = I	1.0 equiv of DCPH	4	19	0.85	58	1.2	4.2	0.70	2.3
17	X = I	10 equiv of DCPH	4	0	13	93	0	0	0	0
18	X = I	1.0 equiv of DCPD (99% d_1)	4	26	0	47 (99% d_1)	2.6	10	1.8	6.2
19	X = I	1.0 equiv of DCPH; 0.15 equiv of PDNB	4	58	tr	21	tr	12	2.4	tr
20	X = I	1.0 equiv of DCPH; 0.20 equiv of lithiopropiophenone	45	76	0	20	0	0	0	0
21	X = I	10 equiv of DCPH; no lithiopropiophenone	24	99	0	0	0			
3	X = Br	none	60	76	0	0	0	20	0.70	0
22	X = Br	1.0 equiv of DCPH	60	79	0	0	0	12	0.70	0

[a] All reactions were carried out at a reactant ratio of 1:2 (alkyl substrate:lithiopropiophenone) and 0.10 M in alkyl substrate at room temperature unless otherwise. [b] Amount relative to alkyl iodide. [c] tr = trace.

wide use as radical traps are 1,4-cyclohexadiene[13,29] (eq 3) and dicyclohexylphosphine[9c,13,29a,30] (eq 4).



The effect of 1,4-cyclohexadiene on the reaction of lithiopropiophenone with 2,2-dimethyl-1-iodo-5-hexene is shown in Table IV. The use of 5 equiv of 1,4-cyclohexadiene (experiment 12) resulted in an increased amount of cyclic hydrocarbon (compound **2**) at the expense of the alkylation products (compounds **4**, **5**, and **6**). When 15 equiv of the diene trap were utilized, the yield of cyclic hydrocarbon increased to 28% (experiment 13). Hence, 1,4-cyclohexadiene is trapping the cyclic radical (**2**-a) at a faster rate than it can disproportionate or be captured by enolate radical (see Scheme III). Furthermore, the ratio of cyclic to straight-chain hydrocarbon (2/1 = 28) indicates that cyclization is faster than trapping by the diene. The fate of 1,4-cyclohexadiene upon trapping radical **2**-a is also shown in Scheme III. For every mole of cyclic hydrocarbon formed, approximately one-half mole of benzene was formed (see Table IV). The decrease in the amount of straight-chain alkylation products in going from experiment 2 to experiments 12 and 13 in part can be explained if more diffusion occurs from the solvent cage as the viscosity of the solvent system decreases with increasing amounts of diene added. The escaped radical can then cyclize and be trapped by the diene. Interestingly, the ratio of straight-chain alkylation products **4**/**5** remains constant in experiments 2, 12, and 13 (Table IV), suggesting that products **4** and **5** arise from a common intermediate. Hence the results using 1,4-cyclohexadiene as a radical trap further support the pathway depicted in Scheme III for the reaction of lithiopropiophenone with the alkyl iodide probe.

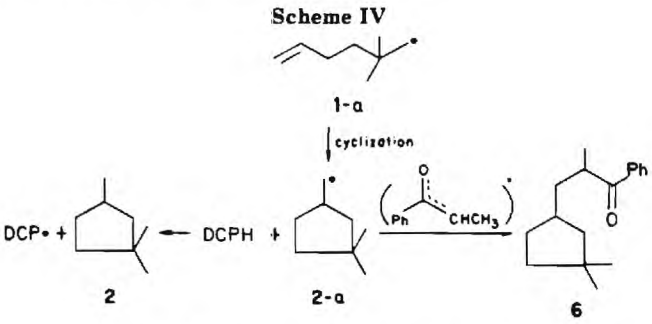
The effects of dicyclohexylphosphine (DCPH) on the reactions of 2,2-dimethyl-1-iodo-5-hexene and 1-bromo-2,2-dimethyl-5-hexene with lithiopropiophenone were also investigated. Experiments 15–17 in Table V indicate the effectiveness of DCPH as a radical trap in the reaction of the alkyl iodide with the lithium enolate. The use of even 1 equiv of DCPH lowers dramatically the yield of straight-chain alkylation products and gives instead a high yield of the cyclic hydrocarbon (experiment 16). When 10 equiv of DCPH are utilized (experiment 17), the only reaction products are hydrocarbons **1** and **2**. As in the case of 1,4-cyclohexadiene, the yield of cyclic hydrocarbon is much higher than the yield of straight-chain hydrocarbon and is due to the observation that radical **1**-a cyclizes at a faster rate than it accepts a hydrogen atom from DCPH.[31] The source of the hydrogen atom was determined to be the P–H bond of DCPH by a deuterium labeling study. For example, when 1 equiv of DCPD (>99% d_1) was used as the hydrogen atom donor, the cyclic hydro-

(29) (a) Kuivila, H. G.; Alnajjar, M. S. *J. Org. Chem.* **1981**, *46*, 1053. (b) Halgren, T. A.; Howden, M. E. H.; Medof, M. E.; Roberts, J. D. *J. Am. Chem. Soc.* **1967**, *89*, 3051. (c) Kira, M.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 3892.

(30) (a) Kuivila, H. G.; Smith, G. F. *J. Org. Chem.* **1980**, *45*, 2918. (b) Smith, G. F.; Kuivila, H. G.; Simon, R.; Sultan, L. *J. Am. Chem. Soc.* **1981**, *103*, 833. (c) Ashby, E. C.; DePriest, R. N. *J. Am. Chem. Soc.* **1982**, *104*, 6144.

(31) The reaction of 1-iodo-2,2-dimethyl-5-hexene with 1.0 M DCPH in HMPA in the presence of a catalytic amount of AIBN at 60 °C gave 74% cyclic hydrocarbon to only 5.5% straight-chain hydrocarbon. These results are similar to Beckwith's data (ref 15) where *n*-Bu_3SnH is used as the hydrogen atom donor. Thus cyclization of radical **1**-a is faster than the rate of trapping by these hydrogen atom donors.

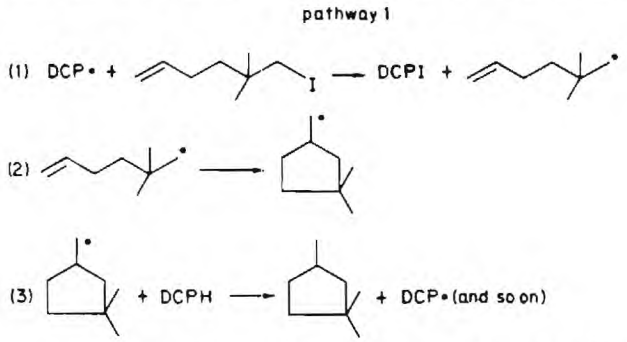
Scheme IV



carbon was found to have 99% deuterium incorporation (experiment 18). Interestingly the use of DCPD led to an increase in alkylation products as compared to DCPH. The increase may be attributed to the deuterium isotope effect where the P–D bond is stronger than the P–H bond and hence the former is a poorer hydrogen atom donor.

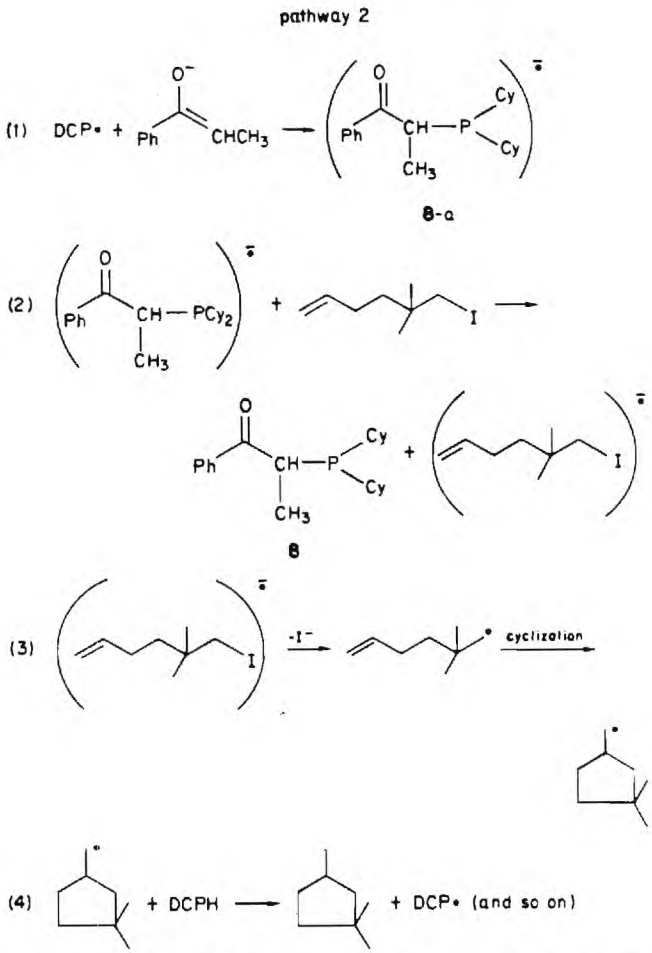
The question of whether DCPH is simply acting as a hydrogen atom donor or in some way playing an additional role in the reaction of lithiopropiophenone with the alkyl iodide was addressed. On the basis of Scheme III it is difficult to rationalize the dramatic effect that DCPH has on the product distribution. Furthermore as shown in experiment 15, the half-life for the reaction of alkyl iodide and enolate is 1 h when 1 equiv of DCPH is present. This represents a tenfold rate acceleration when compared to experiment 1 where no DCPH is present.

Our attempts to explain these results are shown in Scheme IV. Pathway 1 suggests that the DCP· radical



formed upon trapping of the cyclic radical 2-a by DCPH can induce a free-radical chain process. If indeed the free-radical chain reaction is occurring, then both the predominance of cyclic hydrocarbon and the rate acceleration as discussed previously can be rationalized. As a test for this reaction pathway, the reaction of DCPH and alkyl iodide was carried out in the presence of a catalytic amount of lithiopropiophenone (experiment 20). Even when the reaction was allowed to proceed for an extended period of time, the yield of 1,1,3-trimethylcyclopentane (the only product) never exceeded the amount of lithiopropiophenone used. Hence the notion that the lithium enolate is simply functioning as an initiator to a free-radical chain process was ruled out. Thus pathway 1 appears not to be operating since all it requires is a small amount of enolate as an initiator.

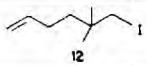
A second scheme can be envisioned to explain the ultimate fate of the DCP· radical formed upon hydrogen atom transfer from DCPH to the cyclic radical 2-a. This scheme is illustrated in pathway 2 and in essence involves the reaction of the DCP· radical with the enolate anion to produce a radical anion. The radical anion 8-a can now transfer an electron to the alkyl iodide to propagate an $S_{RN}1$ radical–radical anion chain process. If pathway 2 is operating, then the comparison of the half-lives of ex-

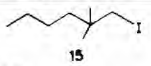


periments 1 and 15 suggests that the radical anion 8-a is about 10 times better an electron-transfer agent than lithiopropiophenone itself. Thus the pathway depicted in Scheme III for the reaction of lithiopropiophenone with alkyl iodide should compete poorly with pathway 2. As a result only a small amount of straight-chain alkylation products should be formed in the presence of 1 equiv of DCPH since the $S_{RN}1$ process should favor cyclization of radical 1-a over random coupling of radicals outside of the solvent cage. The verification of pathway 2 is shown by experiment 19 in Table V. The use of 0.15 equiv of *p*-dinitrobenzene (a good radical anion trap) had an inhibitory effect on the reaction of lithiopropiophenone with the alkyl iodide in the presence of 1 equiv of DCPH as would be expected if the $S_{RN}1$ process depicted in pathway 2 was operating.[2-4] Hence the rate of reaction and product distribution in experiment 19 lies somewhere between the results of experiments 1 and 15. The use of *p*-dinitrobenzene allows the pathway depicted in Scheme III to become more important in the reaction of the enolate with the alkyl iodide and DCPH by virtue of reducing the contribution of pathway 2. Further support for pathway 2 came with the isolation and identification of compound 8 (oxidized during workup) by column chromatography.

The reaction of lithiopropiophenone with 1-bromo-2,2-dimethyl-5-hexene in the presence of 1 equiv of DCPH (experiment 22) gave the same results as experiment 3 where no DCPH was present. Since the reaction of the lithium enolate with the alkyl bromide gives no radical by product (experiment 3), then the formation of DCP· radical from DCPH can not occur to initiate the $S_{RN}1$ chain process depicted by pathway 2. Once again the data indicates that the alkyl bromide is not reacting via an SET pathway.

Table VI. Effect of Double Bond on the Reaction of Lithiopropiophenone with 2,2-Dimethyl-1-iodo-5-hexene (12) in HMPA[a]

expt	alkyl iodide	additives	time, h	% yield 12	1	2	3	4	5	6
2	 12	none	60	8.0	0	1.0	0.88	66	11	1.0

expt	alkyl iodide	additives	time, h	% yield 15	9	10	11
23	 15	none	60	12	3.4	64	10
24	15	1.0 equiv of DCPH[b]	4	25	65	4.1	2.8

[a] All reactions were carried out at a reactant ratio of 1:2 (alkyl iodide:lithiopropiophenone) and 0.10 M in alkyl iodide at room temperature. [b] Amount relative to alkyl iodide.

Effect of the Double Bond in the Alkyl Iodide Probe. In order to ascertain whether the double bond present in the alkyl iodide probe was in some manner perturbing the reaction of the probe with lithiopropiophenone, perhaps by a neighboring group effect, the reaction of 2,2-dimethyl-1-iodohexane (**15**) with the lithium enolate was carried out. A comparison of experiments 2 and 23 in Table VI shows that the double bond of the probe iodide has little effect on either product distribution or reaction rate. Hence the reaction of lithiopropiophenone with the probe can be generalized to any neopentyl type alkyl iodide.

The reaction of lithiopropiophenone with 2,2-dimethyl-1-iodohexane in the presence of 1 equiv of DCPH gave as the major product 2,2-dimethylhexane (experiment 24). Once again the double bond of the alkyl iodide probe has no effect on product distribution or reaction rate as a comparison of experiments 16 and 24 shows. These observations are consistent with pathway 2 of Scheme IV and negate our earlier suggestion[13] that DCPH is trapping radical 1-a via a concerted process[32] to produce the cyclic hydrocarbon.

Conclusion

A variety of methods have been utilized in order to evaluate the occurrence of an electron-transfer pathway in the reaction of lithiopropiophenone with primary alkyl halides and tosylate. The effects of leaving group, solvent, and hydrogen atom donors on product distribution and reaction rate were thoroughly investigated and support SET as the major pathway for reaction of primary (neopentyl type) iodides with enolate anions. Conversely, the alkyl bromide and tosylate appear to be reacting via an S_N2 pathway. Hexamethylphosphoramide has also been shown to be an effective solvent for the alkylation of enolate anions with neopentyl type alkyl iodides at room temperature, whereas, previous attempts to perform these alkylation reactions have failed. Furthermore, the detailed investigation of the effects of dicyclohexylphosphine on the alkylation reactions should better clarify the role that this hydrogen atom donor can play in radical reactions.

Experimental Section

Materials. Solvent-grade pentane, hexane, and benzene were stirred over concentrated H_2SO_4, washed with water, dried over $MgSO_4$, and distilled from CaH_2. Reagent grade diethyl ether, tetrahydrofuran (THF), and benzene were purchased from Fisher and distilled under nitrogen from deep purple solutions of sodium benzophenone ketyl. Hexamethylphosphoramide (HMPA) from Aldrich was fractionally distilled from sodium at reduced pressure. Samples of *n*-decane, 1-heptene, *p*-dinitrobenzene, triphenylmethanol, and *p*-toluenesulfonic acid from Aldrich, hexaphenylditin and di-*tert*-butyl nitroxyl radical from Alfa, and 1,1,3-trimethylcyclopentane and 2,2-dimethylhexane from Wiley Organics were used as received. An authentic sample of 5,5-dimethyl-1-hexene was obtained as previously described.[9c] A sample of 3,3-dimethyl-1-methylenecyclopentane (from experiment 9, Table III) was obtained by preparative GLC (column C) and gave NMR and mass spectra identical with those previously reported for the hydrocarbon.[33]

Acetophenone, propiophenone, diisopropylamine, and 1,4-cyclohexadiene were purchased from Aldrich and distilled from CaH_2 under nitrogen. Reagent grade acetone from Fisher was distilled from P_2O_5 prior to use. Dicyclohexylphosphine (DCPH) from Aldrich was purified by distillation (bp 68–70 °C at 0.04 mmHg), and deuterated dicyclohexylphosphine (DCPD) was prepared as previously described.[34] Methyllithium and *n*-butyllithium were purchased from Aldrich and used after standardization by Eastham–Watson titration.

General Procedures. All glassware and syringes were oven-dried at 150 °C for at least 2 h and cooled under a flow of purified nitrogen just prior to use. Transfer of reagents was performed by using syringes equipped with stainless steel needles. Reactions were carried out in round-bottomed flasks equipped with T-bore stopcocks attached to male 24/40 standard taper joints (allows nitrogen flush while reagents are being added or removed through the stopcock by syringe) and a Teflon-coated magnetic stirring bar.

Proton NMR spectra were recorded on either a Varian T-60A or Bruker WM-300 instrument with chemical shifts reported relative to Me_4Si. Mass spectral analyses were performed on a Varian MAT-112S spectrometer. IR spectra were recorded on a Perkin-Elmer 299 infrared spectrophotometer. Elemental compositions were determined either by microanalysis (Atlantic Microlabs, Inc. of Atlanta, GA) or by high-resolution mass spectrometry.

Quantitative gas–liquid chromatographic (GLC) analyses were conducted on a Hewlett-Packard Model 700 instrument equipped with an automatic integrator and a flame ionization detector. GLC yields were determined by using internal standards and comparing peak areas which were corrected for response factors. Preparative GLC separations were performed on a F&M Model 720 instrument equipped with a thermal conductivity detector. For quantitative GLC analyses, the following columns and conditions were used (retention times are given relative to the internal standard): column A, 10% Apiezon L on Chromosorb P, 4 ft × $^1/_8$ in., 95 °C, *n*-decane (1.00), 1-bromo-2,2-dimethyl-5-hexene (1.43), 2,2-dimethyl-1-iodo-5-hexene (2.95), 2,2-dimethyl-1-iodohexane (3.04);

(32) Walling, C.; Cooley, J. H.; Ponaras, A. A.; Racah, E. J. *J. Am. Chem. Soc.* **1966**, *88*, 5361.

(33) Adlercreutz, P.; Masnusson, G. *Acta Chem. Scand., Ser. B* **1980**, *B34*, 647.

(34) Ashby, E. C.; DePriest, R. N.; Su, W. Y. *Organometallics* **1984**, *3*, 1718.

column B, 10% SE-30 on Chromosorb W, 1.5 ft × 1/8 in., 115 °C, *p*-chlorobenzophenone (1.00), 2,2-dimethyl-1-tosyl-5-hexene (2.34); column C, 8% Apiezon L on Chromosorb P, 20 ft × 1/8 in., 60 °C, benzene (0.89), 1-heptene (1.00), 5,5-dimethyl-1-hexene (1.19), 2,2-dimethylhexane (1.29), 1,1,3-trimethylcyclopentane (1.43), 3,3-dimethyl-1-methylenecyclopentane (1.67); column D, 5% Carbowax 20M on Chromosorb G, 4 ft × 1/4 in., 135 °C, propiophenone (0.44), mesityl *tert*-butyl ketone (1.00), **10** (1.29), **4** (1.65), **11** (2.57), **5** (3.39), **6** (3.93).

Preparations. 2,2-Dimethyl-5-hexen-1-ol, 1-Bromo-2,2-dimethyl-5-hexene, 2,2-Dimethyl-1-iodo-5-hexene, and 2,2-Dimethyl-1-tosyl-5-hexene. The alcohol was prepared by the method of Beckwith[35] and exhibited the following: ^{1}H NMR (CCl_4) δ 0.83 (s, 6 H), 0.85–2.40 (m, 5 H, contains OH), 3.25 (s, 2 H), 4.75–6.20 (m, 3 H). From the alcohol, the corresponding alkyl bromide, iodide, and tosylate were prepared by previously described methods.[9c]

2,2-Dimethyl-1-iodohexane. A 2-L flask was charged with 1.4 mol of *n*-BuLi in 1100 mL of hexane. After cooling the flask to −5 °C and with stirring, 95 g (1.6 mol) of acetone in 100 mL of dry hexane was added dropwise over a 1-h period. The reaction mixture was then stirred for an additional 0.5 h as it warmed to 25 °C, quenched with 1 M HCl (100 mL), and extracted twice with Et_2O. The combined ethereal layers were washed with saturated $NaHCO_3$ followed by brine, dried, and concentrated to give 140 g (86%) of crude 2-methyl-2-hexanol. From the alcohol, the title compound was prepared (14% overall) by an analogous route used for the preparation of 2,2-dimethyl-1-iodo-5-hexene and gave the following: bp 64–66 °C (3.0 mmHg); ^{1}H NMR (CCl_4) δ 0.90–1.4 (m, 9 H), 1.0 (s, 6 H), 3.1 (s, 2 H); IR (CCl_4) 2960, 1460, 1420, 1380, 1360, 1245, 1150, 860, 690 cm^{-1}; mass spectrum, *m/e* (relative intensity) 240 (M^+, 0.3), 183 (6) 113 (31), 71 (75), 57 (100), 55 (34). Anal. Calcd for $C_8H_{17}I$: C, 40.01; H, 7.15. Found: C, 40.19; H, 7.12.

2,2-Dimethyl-5-hexenal. In a 250-mL, round-bottomed flask fitted with a reflux condenser were suspended 16 g (73 mmol) of pyridinium chlorochromate and 1.1 g (14 mmol) of sodium acetate in 100 mL of anhydrous CH_2Cl_2. 2,2-Dimethyl-5-hexen-1-ol (6.2 g, 48 mmol) in 20 mL of CH_2Cl_2 was added in one portion to the magnetically stirred solution. After 2 h, the reaction mixture was worked up as previously described.[36] The residual oil was stirred over CaH_2 for 2 h, filtered, and then fractionally distilled to give 3.6 g (60%) of aldehyde (bp 63–64 °C at 17 mmHg) which gave NMR and IR spectra identical with those previously reported for the aldehyde.[37]

4,4-Dimethyl-1-phenyl-2,7-octadien-1-one. To a cold (−78 °C) solution of LDA, from 29 mmol of MeLi, 32 mmol of diisopropylamine, and 30 mL of Et_2O, was added dropwise and with stirring during 15 min, 3.5 g (29 mmol) of acetophenone in 10 mL of Et_2O. The resulting solution was stirred at −78 to −40 °C for 1 h and then 3.6 g (29 mmol) of 2,2-dimethyl-5-hexenal was added dropwise and with stirring during 5 min. The resulting pale yellow solution was stirred at −40 to 0 °C for 1 h and then 50 mL of ice-cold 1 M HCl was added. The mixture was extracted with Et_2O and the combined ethereal extracts were washed successively with 1 M HCl, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated to give 6.5 g of crude ketol. To the crude ketol in a 250-mL round-bottomed flask was added 200 mL of benzene and 0.260 g (1.36 mmol) of *p*-TsOH. The flask was fitted with a Dean–Stark trap and condenser and the benzene was refluxed for 30 min. The solution was then cooled, washed twice with saturated $NaHCO_3$ and then brine, dried over $MgSO_4$, and concentrated. The residual liquid was then fractionally distilled to give 4.7 g (72%) of enone (bp 114–116 °C at 0.10 mmHg): ^{1}H NMR (CCl_4) δ 1.0 (s, 6 H), 1.2–2.2 (m, 4 H), 4.8–6.2 (m, 3 H), 6.9 (d, 1 H), 7.2–8.0 (m, 6 H); IR (film) 3065, 2960, 1665, 1615, 1445, 1300, 1220, 1020, 910, 700 cm^{-1}; mass spectrum, *m/e* (relative intensity) 228 (M^+, 2), 157 (23), 105 (100), 91 (15), 77 (54), 51 (16), 43 (30), 41 (27). Anal. Calcd for $C_{16}H_{20}O$: C, 84.15, H, 8.84. Found: C, 83.99; H, 8.86.

1-Phenyl-2,4,4-trimethyl-7-octen-1-one (5). A solution of lithium in liquid ammonia was prepared by the addition of freshly cut lithium wire (0.0267 g, 3.85 mmol) to liquid ammonia (40 mL, distilled from sodium) and stirred 15 min. 4,4-Dimethyl-1-phenyl-2,7-octadien-1-one (0.400 g, 1.75 mmol) and Ph_3COH (0.455 g, 1.75 mmol) in 10 mL of anhydrous Et_2O were added dropwise. The reaction mixture was stirred 30 min and then diluted with 30 mL of Et_2O, and 1.49 g (10.5 mmol) of methyl iodide in 5.0 mL of Et_2O was then added dropwise. After 30 min the solution was worked up by a previously described method.[38] The residual liquid was chromatographed on silica gel with a hexane–ether eluent (96:4 v/v) to give 0.26 g (60%) of the ketone. Bulb-to-bulb distillation afforded the ketone as a colorless liquid: ^{1}H NMR (CCl_4) δ 0.85 (s, 6 H), 1.2 (d, 3 H, *J* = 7.0 Hz), 1.2–2.2 (m, 6 H), 3.6 (m, 1 H), 4.8–6.2 (m, 3 H), 7.4–8.0 (m, 5 H); IR (film) 3065, 2960, 1680, 1640, 1595, 1450, 1215, 970, 910, 710 cm^{-1}; mass spectrum, *m/e* (relative intensity) 244 (M^+, 0.5), 189 (4), 147 (31), 105 (100), 77 (23), 55 (22). Anal. Calcd for $C_{17}H_{24}O$: C, 83.54; H, 9.92. Found: C, 83.64; H, 9.94.

1-Phenyl-2,4,4-trimethyl-1-octanone (11). To the crude product (0.80 g) of the lithium ammonia reduction/methylation reaction was added 60 mL of absolute ethanol in a 100-mL, round-bottomed flask. This was followed by the addition of 80 mg of 5% Pd on C. The mixture was then hydrogenated at 1 atm and 25 °C for 3 h. After being filtered and concentrated, the residual liquid was chromatographed on silica gel with a hexane–ether eluent (99:1 v/v) to give 0.22 g (51%) of the ketone. Distillation (bulb to bulb) afforded the ketone as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 0.78, 0.81 (s, 6 H), 0.86 (t, 3 H, *J* = 6.6 Hz), 1.2 (d, 3 H, *J* = 7.0 Hz), 1.2–1.3 (m, 8 H), 3.6 (m, 1 H), 7.4–8.0 (m, 5 H); IR (film) 3060, 2960, 1680, 1595, 1455, 1215, 970, 795, 710 cm^{-1}; mass spectrum, *m/e* (relative intensity) 246 (M^+, 1), 189 (5), 147 (22), 105 (100), 77 (13), 57 (12). Anal. Calcd for $C_{17}H_{26}O$: C, 82.85; H, 10.66. Found: C, 82.87; H, 10.65.

3-(3,3-Dimethylcyclopentyl)-2-methyl-1-phenyl-1-propanone (6). To a cold (−78 °C) solution of LDA, from 63 mmol of MeLi, 66 mmol of diisopropylamine, and 40 mL of Et_2O, was added dropwise and with stirring during 15 min, 8.4 g (63 mmol) of propiophenone. The resulting solution was stirred at −78 °C for 1 h and then brought slowly to room temperature under vacuum to remove the solvent. The lithium enolate was then redissolved in 40 mL of THF containing 1.5 g (2.1 mmol) of hexaphenylditin, and 1.0 g (4.2 mmol) of 2,2-dimethyl-1-iodo-5-hexene was then added. The resulting solution was irradiated in a 200-mL Pyrex flask with a water-cooled 450-W high pressure Hanovia lamp for 20 h, and then 1.5 g of hexaphenylditin in 30 mL of THF was added to the flask and the irradiation was continued for an additional 20 h. The reaction mixture was then quenched with 1 M HCl (30 mL) and extracted twice with hexane. The combined hexane layers were washed successively with 1 M HCl and brine, dried, and concentrated. The residual liquid (10 g) was chromatographed on silica gel (950 g) with a hexane–ether eluent (99:1 v/v). Concentration of the fractions containing the cyclic alkylation product gave approximately 3 g of a crude liquid. The liquid was rechromatographed under the same conditions to give, after concentration of the appropriate fractions, 1.1 g of a liquid. GLC analysis (column D) of the liquid resulted in a GC trace containing two peaks: 80% propiophenone to 20% cyclic alkylation product. The mixture was then subjected to preparative GLC (5% Carbowax 20M on Chromosorb G, 1.5 ft, 155 °C) to give 0.20 g (20%) of alkylation product. Distillation (bulb to bulb) afforded the ketone as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 0.89, 0.91, 0.97, 0.98 (s, 6 H), 1.2 (d, 3 H, *J* = 6.9 Hz), 1.2–2.0 (m, 9 H) 3.5 (hextet, 1 H, *J* = 6.9 Hz), 7.3–8.0 (m, 5 H); IR (film) 3065, 2945, 2865, 1685, 1600, 1460, 1365, 1225, 975, 710 cm^{-1}; electron-impact mass spectrum *m/e* (relative intensity) 147 (5), 134 (82), 133 (17), 106 (9), 105 (100), 77 (40), 69 (7), 55 (22), 41 (17); chemical-ionization mass spectrum, *m/e* 245 ($M^+ + 1$). Anal. Calcd for $C_{17}H_{24}O$: C, 83.54; H, 9.92. Found: C, 83.36; H, 9.92.

1-((2,2-Dimethyl-5-hexenyl)oxy)-1-phenyl-1-propene (4). A solution of lithiopropiophenone (19 mmol) in Et_2O was prepared as described above. Upon evaporation of the solvent in vacuo, the lithium enolate was redissolved in 35 mL of HMPA, and 3.0

(35) Beckwith, A. L. J.; Lawrence, T. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1535.
(36) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(37) House, H. O.; Liang, W. C.; Weeks, P. D. *J. Org. Chem.* **1974**, *39*, 3102.
(38) Smith, H. A.; Huff, B. J. L.; Powers, W. J.; Caine, D. *J. Org. Chem.* **1967**, *32*, 2851.

g (13 mmol) of 2,2-dimethyl-1-iodo-5-hexene was added. The reaction mixture was stirred for 60 h at 25 °C, quenched with saturated NH_4Cl (20-mL), and extracted twice with hexane. The combined hexane layers were washed with saturated $NaHCO_3$ followed by five successive washings with water and then dried and concentrated. The residual liquid was chromatographed on silica gel with a hexane–ether eluent (99:1 v/v) to give 1.8 g (57%) of enol ether. Bulb-to-bulb distillation afforded the enol ether as a colorless liquid: ^1H NMR (CCl_4) δ 0.98 (s, 6 H), 1.2–2.2 (m, 4 H), 1.8 (d, 3 H, J = 6.8 Hz), 3.2 (s, 2 H), 4.8–6.2 (m, 4 H), 7.1–7.5 (m, 5 H); IR (film) 3070, 2960, 1655, 1635, 1320, 1065, 910, 760, 700 cm^{-1}; mass spectrum, m/e (relative intensity) 244 (M^+, 4), 202 (8), 135 (28), 134 (100), 133 (75), 117 (19), 105 (41), 91 (9), 77 (15), 69 (59), 55 (46), 41 (48); exact mass calcd for $C_{17}H_{24}O$ 244.1827, found 244.1836.

1-((2,2-Dimethylhexyl)oxy)-1-phenyl-1-propene (10). The enol ether was prepared in 56% yield from 2,2-dimethyl-1-iodohexane by the method described above and after purification gave the following: ^1H NMR (CCl_4) δ 0.97 (s, 6 H), 0.85–1.5 (m, 9 H), 1.8 (d, 3 H, J = 6.8 Hz), 3.2 (s, 2 H), 5.2 (q, 1 H, J = 6.8 Hz), 7.1–7.5 (m, 5 H); IR (film) 3045, 2960, 1650, 1315, 1060, 760, 700 cm^{-1}; mass spectrum, m/e (relative intensity) 246 (M^+, 3), 217 (11), 135 (12), 134 (100), 133 (50), 117 (12), 105 (21), 77 (9), 71 (23), 57 (39), 43 (37); exact mass calcd for $C_{17}H_{26}O$ 246.1984, found 246.1988.

2-(Dicyclohexylphosphino)-1-phenyl-1-propanone. A solution of lithiopropiophenone (9.4 mmol) in HMPA (20 mL) was prepared as described above and 1.2 g (6.3 mmol) of DCPH followed by 1.5 g (6.3 mmol) of 2,2-dimethyl-1-iodo-5-hexene were added. The reaction mixture was stirred for 24 h at 25 °C, quenched with saturated NH_4Cl (10 mL), and extracted twice with hexane. The combined hexane layers were washed 5 times with water, dried, and then concentrated. The residue was chromatographed on silica gel with an ethyl acetate–acetone eluent (1:1 v/v) to give 0.74 g (34%) of the ketone as a viscous oil which was dried in a vacuum dessicator and gave the following: ^1H NMR ($CDCl_3$) δ 1.0–2.1 (br m, 22 H), 1.5 (dd, 3 H), 4.2 (dq, 1 H), 7.3–8.0 (m, 5 H); IR (CCl_4) 3060, 2940, 2860, 1675, 1445, 1170 cm^{-1}; mass spectrum, m/e (relative intensity) 346 (M^+, 8), 264 (28), 263 (30), 182 (27), 133 (14), 117 (100), 105 (30), 83 (24), 77 (25), 55 (57), 43 (27), 41 (50); exact mass calcd for $C_{21}H_{31}O_2P$ 346.2062, found 346.2079.

General Procedure for Alkylation Reactions. Lithiopropiophenone (1.0 mmol) in 5.0 mL of HMPA was prepared as described above and 0.50 mmol of alkyl halide or tosylate was added to the stirring enolate solution at 25 °C. Whenever an additive was employed, the appropriate amount was added to the enolate solution just prior to the addition of the alkyl halide. The alkylation reactions were followed by taking 0.50-mL aliquots from the reaction mixtures at various time intervals and quenching them with saturated NH_4Cl in glass vials containing the necessary internal standards. The organic layer was then extracted (2 × 2.0 mL) with pentane and the combined pentane layers were washed 5 times with H_2O. GLC analyses were then conducted on columns A–D and all products were identified from their GLC retention times and mass spectra by comparison with authentic samples.

Acknowledgment. We are indebted to the National Science Foundation Grant No. CHE 78-00757 for financial support of this work. We also acknowledge stimulating discussions with Professor C. L. Liotta and helpful suggestions concerning product isolation from Dr. J. Hrabie.

Registry No. **2**, 4516-69-2; **4**, 97467-22-6; **5**, 89746-00-9; **6**, 89746-01-0; **9**, 590-73-8; **10**, 97467-24-8; **11**, 97467-25-9; **15**, 97467-23-7; DCPD, 91523-73-8; DCPH, 829-84-5; PDNB, 100-25-4; CH_2=$CH(CH_2)_2C(CH_3)_2CH_2I$, 77400-57-8; CH_2=$CH(CH_2)_2C(CH_3)_2CH_2Br$, 56068-49-6; CH_2=$CH(CH_2)_2C(CH_3)_2CH_2OTs$, 89745-98-2; $(t\text{-}Bu)_2NO$, 2406-25-9; CH_2=$CH(CH_2)_2C(CH_3)_2CH_2OH$, 56068-50-9; BuLi, 109-72-8; $CH_3C(O)CH_3$, 67-64-1; $CH_3(CH_2)_3C(OH)(CH_3)_2$, 625-23-0; CH_2=$CH(CH_2)_2C(CH_3)_2CHO$, 52278-99-6; CH_2=$CH(CH_2)_2C(CH_3)_2CH$=$CHC(O)Ph$, 97467-26-0; $PhC(O)CH_3$, 98-86-2; CH_2=$CH(CH_2)_2C(CH_3)_2CH(OH)CH_2C(O)Ph$, 97467-27-1; $PhC(O)CH_2CH_3$, 93-55-0; lithiopropiophenone, 70887-62-6; 1,4-cyclohexadiene, 628-41-1; 2-(dicyclohexylphosphino)-1-phenyl-1-propanone, 97467-28-2.

Journal of Organometallic Chemistry, 292 (1985) 29–37
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands

NEW METHODOLOGY IN DETERMINING EVIDENCE FOR SINGLE ELECTRON TRANSFER IN THE REACTION OF GRIGNARD REAGENTS WITH KETONES *

YUNSHI ZHANG **, BERND WENDEROTH, WEI-YANG SU, and E.C. ASHBY*
School of Chemistry, Georgia Institute of Technology, Atlanta, GA 30332 (U.S.A)
(Received December 17th, 1984)

Summary

A new method is reported to determine the existence of single electron transfer in the reaction of Grignard reagents with ketones. The method involves the determination of pseudo-first order rate constants by following the rate of disappearance of the paramagnetic intermediate and relating the rate of this disappearance to the appearance of product. The reactions of methyl-, phenyl- and t-butyl-Grignard reagents with substituted benzophenones were examined. This method should be applicable to a wide range of organometallic reactions.

Introduction

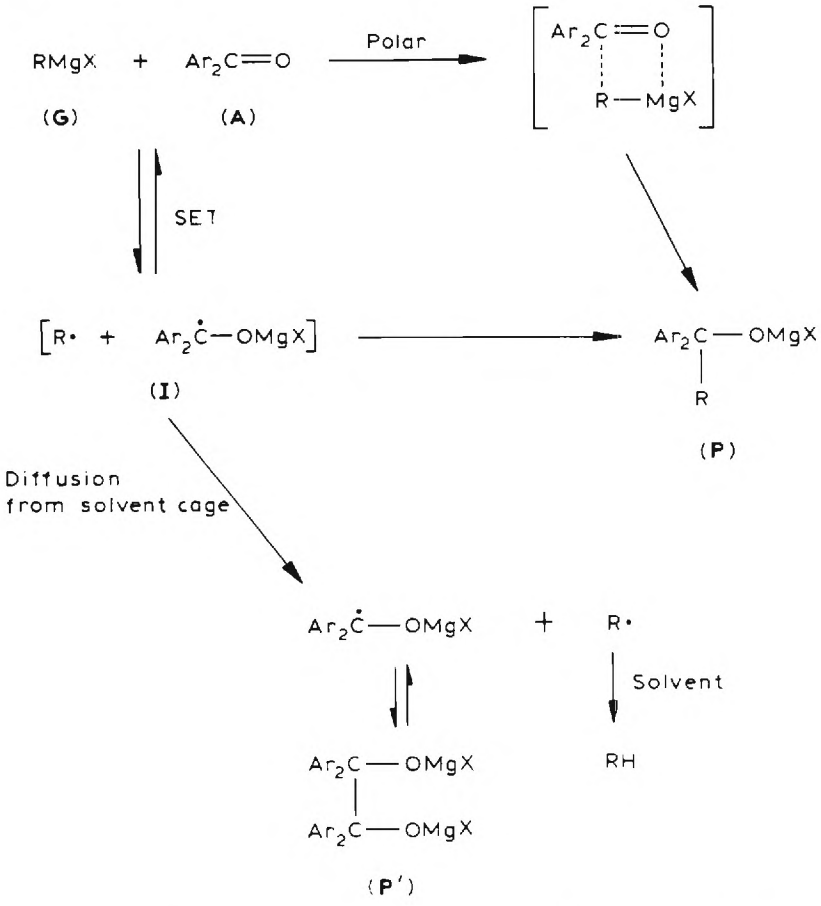
The importance of Grignard reagents in synthetic organic chemistry is well recognized and the mechanisms of reactions with organic substrates have been under investigation by numerous investigators [1–4]. In 1968 Fauvarque and in 1969 Blomberg and Mosher [5,6], presented evidence supporting a SET pathway in the reaction of Grignard reagents with ketones. A few years later Holm [7] proposed a mechanism similar to that proposed by Fauvarque and Blomberg–Mosher and presented strong supporting arguments based on linear free energy studies. His conclusions were broader than previous workers stating that t-butyl Grignard reagents react with aromatic ketones via a SET process and methyl Grignard reagents react via a polar process. More recently, Okubo has presented convincing evidence for the intermediacy of ketyl radicals in the reactions of Grignard reagents with ketones [8–10].

Our research group has focussed on the mechanism of Grignard Compound addition to ketones for two decades [1]. Prior to 1972, we had established that both

* Dedicated to Professor Oleg Reutov on the Occassion of his 65th Birthday on September 5, 1985.
** Visiting scholar, Peoples Republic of China.

0022-328X/85/$03.30

RMgX and R_2Mg species exist in solution and thus both species are capable of reacting with carbonyl compounds. We also established that mechanistic studies involving Grignard reagent addition to organic substrates should be carried out using Grignard reagents (particulary the bromides) at low concentration in order to avoid the existence of higher associated species in solution which when not avoided in the past resulted in unresolvable kinetic analysis. More recently we have been able to show by means of cyclizable free radical probes that indeed free radicals are involved in the reaction of 1°, 2° and 3° Grignard reagents with aromatic ketones [2,3]. Today, based on the work of others and own studies [2,3,12,13], we suggest that the reaction of Grignard reagents (1°, 2°, and 3°) with aromatic ketones is best represented as proceeding via a single electron transfer (SET) pathway at least to some extent depending on the nature of the Grignard reagent, the ketone, and the solvent (Scheme 1).



Sometime ago we reported a kinetic study of the reaction of Grignard reagents with aromatic ketones by following the disappearance of the UV absorption band formed as a result of the complex between the Grignard reagent and the ketone [13]. However, no one has reported using epr techniques to establish the single electron transfer nature of Grignard reactions by observing the rate of disappearance of the

paramagnetic intermediate and relating it to the appearance of product. In view of the fact that this technique would provide a much simpler method for determining SET in a particular reaction than has been used heretofore, we would now like to report studies which indicate that the rate constant of the Grignard reaction can be obtained by following the rate of disappearance of the paramagnetic intermediate and this rate constant related to the rate constant obtained for the appearance of product. Because of the complicated nature of the Grignard reagent-substrate mixture, the most useful and reliable method to obtain kinetic results has been to employ pseudo-first order conditions with the Grignard reagent present in excess [4]. In this situation, the concentration of Grignard reagent is virtually unchanged during the reaction. If the concentration of the paramagnetic intermediate is found to decrease during the same time period that the product is being formed, then an electron transfer process is at least consistent with the data.

Results and discussion

Reaction of methylmagnesium bromide with 2-methylbenzophenone

For many years, the reaction of methyl Grignard reagents with ketones was not easily interpreted in terms of the nature of alkyl transfer in that many reactions showed some of the characteristics of both polar and SET pathways [12]. Recently, we have reported that not only tertiary Grignard reagents, but also primary Grignard reagents react with aromatic ketones in both diethyl ether and THF by an ET process [3], although aliphatic ketones appear to react by a polar process. Such a result is reasonable when one considers that aromatic ketones are much more easily reduced than aliphatic ketones. Although the detection of an SET pathway has been a somewhat difficult task, and detection of free radicals does not necessarily mean that the reaction is proceeding by an SET pathway, we now report that detection and reaction rate determinations of radical reactions by ESR spectroscopy provide evidence for SET pathways in organometallic reactions.

When a 10 fold excess of methyl magnesium bromide (**1**), was allowed to react with 2-methylbenzophenone (**2**) in ether at room temperature, a light pink color developed rapidly and the solution was found to be EPR active. The intensity of the EPR signal increased rapidly to a maximum (ca. 0.01% relative to the initial concentration of ketone [14]) then decreased slowly in a first order fashion (Table 1.

TABLE 1

EPR-STUDY FOR THE REACTION OF CH_3MgBr WITH 2-METHYLBENZOPHENONE IN ETHER AT ROOM TEMPERATURE [a,b]

Entry	Time (min)	EPR-Intensity (mm)	ln EPR-Intensity
1	2.5	174	5.169
2	4.0	147	4.990
3	5.5	122	4.804
4	7.0	95	4.554
5	8.5	69	4.234
6	10.0	52	3.951

[a] The initial concentrations were 0.066 *M* for the ketone and 0.066 *M* for the Grignard reagent. [b] The maximum concentration of radical intermediate was ca. 0.01/%.

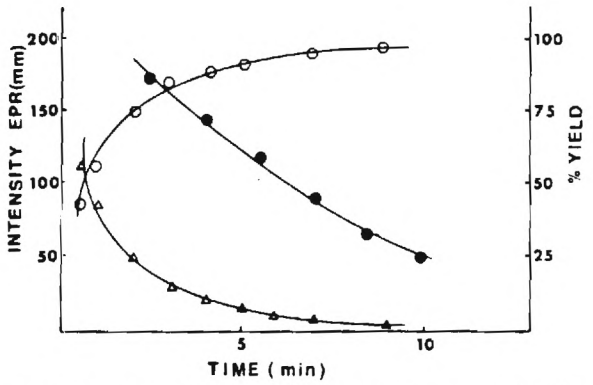


Fig. 1. Reaction of 2-methylbenzophenone with a 10 fold excess of CH_3MgBr in ether at room temperature: (●) intensity of the EPR signal (mm) vs. time (min) (△) recovered ketone(%) vs. time; (○) products(%) vs. time.

Fig. 1). A reaction profile study, as a function of time, has been also carried out indicating the rate of formation of the product and disappearance of the ketone (Table 2). It is shown that the rate of disappearance of ketone (formation of the product) exhibits pseudo-first order behavior (Fig. 1). Expectedly, the concentration of the product is increasing as a function of time, whereas, the concentration of the paramagnetic intermediate is decreasing during the same time period. However, the Grignard reaction can be simply described as in eq. 1 in which **G** is in excess. Based on the reaction profile study, the rate expression of the reaction would be as shown

$$\mathbf{A} + \mathbf{G} \overset{K}{\rightleftharpoons} \mathbf{I} \overset{k}{\rightarrow} \mathbf{P} \tag{1}$$

A = Ketone K = equilibrium constant **P** = product
G = Grignard reagent **I** = paramagnetic intermediate

$$\frac{-\mathrm{d}[\mathbf{A}]}{\mathrm{d}t} = \frac{\mathrm{d}[\mathbf{P}]}{\mathrm{d}t} = k_{\text{profile}}\{[\mathbf{P}_\infty] - [\mathbf{P}]\} \tag{2}$$

TABLE 2

REACTION PROFILE STUDY OF THE REACTION OF CH_3MgBr WITH 2-METHYLBENZOPHENONE IN ETHER AT ROOM TEMPERATURE [a,b,c]

Entry	Time (min)	Carbinol (%)	Ketone	$\ln(\mathbf{P}_\infty - \mathbf{P}_t)$
1	0.5	44	57	4.043
2	1	56	44	3.784
3	2	74	26	3.258
4	3	85	15	2.708
5	4	89	11	2.398
6	5	92	8	2.079
7	7	96	4	1.386
8	9	98	2	0.693

[a] The initial concentration was 0.066 *M* for the ketone and 0.66 *M* for Grignard reagent. [b] The percent rates were determined by GLC using 9-fluorenone as the internal standard. [c] Yields were normalized.

Assume that: $[\mathbf{A}] + [\mathbf{I}] + [\mathbf{P}] = [\mathbf{A}_0] = [\mathbf{P}_\infty]$ then:

$$\frac{-\mathrm{d}[\mathbf{A}]}{\mathrm{d}t} = \frac{\mathrm{d}[\mathbf{P}]}{\mathrm{d}t} = k_{\text{profile}}\{[\mathbf{A}] + [\mathbf{I}]\} \tag{3}$$

$$\frac{-\mathrm{d}[\mathbf{A}]}{\mathrm{d}t} = \frac{\mathrm{d}[\mathbf{P}]}{\mathrm{d}t} = k_{\text{profile}}[\mathbf{A}] \tag{4}$$

in eq. 2. Since the concentration of the radical intermediate **I** is very small (i.e. $[\mathbf{I}] \approx 0$), eq. 3 can then be simplified to eq. 4. On the other hand, based on the EPR study, the rate expression of the reaction is shown in eq. 5–10.

$$\frac{-\mathrm{d}[\mathbf{I}]}{\mathrm{d}t} = k_{\text{EPR}}[\mathbf{I}] \tag{5}$$

$$K = \frac{[\mathbf{I}]}{[\mathbf{A}][\mathbf{G}]} \tag{6}$$

$$[\mathbf{I}] = K[\mathbf{A}][\mathbf{G}] \tag{7}$$

In the pseudo-first order reaction, [**G**] is a constant. Therefore:

$$\frac{-\mathrm{d}[\mathbf{I}]}{\mathrm{d}t} = K[\mathbf{G}]\frac{\mathrm{d}[\mathbf{A}]}{\mathrm{d}t} \tag{8}$$

$$-\mathrm{K}[\mathbf{G}]\frac{\mathrm{d}[\mathbf{A}]}{\mathrm{d}t} = k_{\text{EPR}}\mathrm{K}[\mathbf{G}][\mathbf{A}] \tag{9}$$

$$\frac{-\mathrm{d}[\mathbf{A}]}{\mathrm{d}t} = k_{\text{EPR}}[\mathbf{A}] = \frac{\mathrm{d}[\mathbf{P}]}{\mathrm{d}t} \tag{10}$$

Therefore, comparing eq. 4 with 10, the rate constants in both methods should be consistent with each other (i.e. $k_{\text{profile}} \approx k_{\text{EPR}}$). The pseudo-first order rate constant for the radical intermediate decay process observed by EPR spectroscopy (Table 1) has been calculated to be $k_{\text{EPR}} = 2.7 \times 10^{-3}\ \text{s}^{-1}$ (correlation coeff. = −0.9932). The pseudo-first order rate constant of this reaction observed from the reaction profile by following the formation of the product ($\mathbf{P}_\infty - \mathbf{P}_t$) is $k_{\text{profile}} = 6.5 \times 10^{-3}\ \text{s}^{-1}$ (correlation coeff. = −0.9941). These two rate constants do not match perfectly possibly because the equilibrium between the reactants and paramagnetic intermediate is being reached late. Therefore, the observed rate constant obtained by EPR spectroscopy (k_{EPR}) is smaller. In fact, the two rate constants (k_{EPR} and k_{profile}) are closer when the data are taken after the equilibrium has been reached (i.e. the latter stage of the reaction 2.7 and $5.6 \times 10^{-3}\ \text{s}^{-1}$). It is, of course,also possible that the difference between these two observed rate constants may be due to a competition between the ET and polar processes being involved in the reaction pathway. Nevertheless, these kinetic data and the observation that the rate of disappearance of the paramagnetic intermediate is related to the rate of appearance of product supports the suggestion that the reaction of methylmagnesium bromide with benzophenone proceeds via a single electron transfer pathway.

Reaction of phenylmagnesium bromide with 2-methylbenzophenone

Since the reactions of substituted benzophenone with phenylmagnesium bromide have been well established as proceeding via an ET pathway [8–10], this reaction should be a good model system to examine the relationship between k_{EPR} and

TABLE 3

EPR-STUDY FOR THE REACTION OF C_6H_5MgBr WITH 2-METHYLBENZOPHENONE IN ETHER AT ROOM TEMPERATURE [a,b]

Entry	Time (min)	EPR-Intensity (mm)	ln EPR-Intensity
1	2.5	194	5.268
2	4.0	138	4.927
3	5.5	100	4.605
4	7.0	75	4.317
5	8.5	59	4.077
6	10.0	49	3.892

[a] The initial concentrations were 0.066 *M* for the ketone and 0.66 *M* for Grignard reagent. [b] The maximum concentration of radical intermediate was ca. 0.01% [14].

$k_{profile}$. When an excess (10 fold) of phenylmagnesium bromide (**3**) was allowed to react with 2-methylbenzophenone in ether at room temperature, a purple color developed rapidly and the solution was found to be EPR active. As in the case of the methyl-Grignard reagent, the intensity of the EPR signal increased rapidly to a maximum (ca. 0.01% relative to the initial concentration of ketone [14]) then decreased slowly in a first order fashion (Table 3, Fig. 2) with $k_{EPR} = 3.1 \times 10^{-3}$ s^{-1} (correlation coeff. = −0.9945). The data for the reaction profile as a function of time are given in Table 4. The profile of the disappearance of the ketone (formation of products in which we assume that both carbinol and pinacol come from the same intermediate) was consistent with pseudo-first order behavior with $k_{profile} = 5.1 \times 10^{-3}$ s^{-1} (correlation coeff. = −0.9920). These two rate constants (k_{EPR} and $k_{profile}$) are comparable. As mentioned previously, the two rate constants match better when the data are taken from the latter stage of the reaction where the equilibrium between reactants and paramagnetic intermediate has been reached. As expected, the rate constant of the reaction taken from the latter stage (entries 3–8, Table 4) during the time period where the EPR study is performed is $k'_{profile} = 3.6 \times 10^{-3}$ s^{-1} (correlation coeff. = −0.9944). Indeed, these two rate constants ($k'_{profile}$ and k_{EPR}) are the same within experimental error (3.6×10^{-3} s^{-1} vs. 3.1×10^{-3} s^{-1}). Once again, the data provide supporting evidence for the description of the reaction of

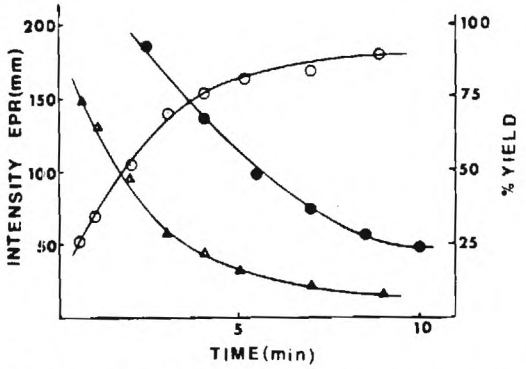


Fig. 2. Reaction of 2-methylbenzophenone with a 10 fold excess of C_6H_5MgBr in ether at room temperature: (●) intensity of the EPR signal (mm) vs. time, (min); (△) recovered ketone(%) vs. time; (○) product (%) vs. time.

TABLE 4

REACTION PROFILE STUDY OF THE REACTION OF C_6H_5MgBr WITH 2-METHYLBENZOPHENONE IN ETHER AT ROOM TEMPERATURE [a,b,c]

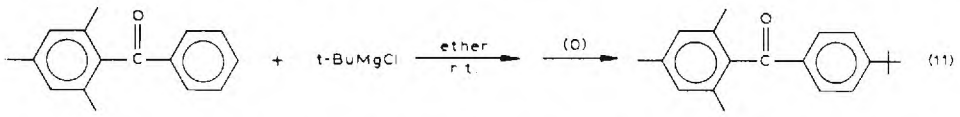
Entry	Time (min)	Product(%) [d]	Ketone (%)	ln ($P_\infty - P_t$)
1	0.5	26	74	4.304
2	1	34	66	4.190
3	2	53	47	3.850
4	3	71	29	3.367
5	4	77	23	3.135
6	5	83	17	2.833
7	7	89	11	2.398
8	9	92	8	2.079

[a] The initial concentrations were 0.066 *M* for the ketone and 0.66 *M* for Grignard reagent. [b] The percent yield were determined by NMR using 2-t-butylanthraquinone as standard. [c] Yields were normalized. [d] Carbinol and pinacol.

phenylmagnesium bromide with benzophenone as an SET process and the rate of disappearance of the paramagnetic intermediate is realted to the rate of appearance of products (disappearance of the ketone) (Fig. 2).

Reaction of t-butylmagnesium chloride (4) with substituted benzophenones

Reaction of t-butylmagnesium chloride (**4**) with benzophenone has been well studied in the past. It is known that the reaction proceeds mainly via a SET pathway [3]. When 2,4,6-trimethylbenzophenone (**5**) was allowed to react with a 10 fold excess of **4** in ether at room temperature, a purple color developed rapidly and the solution was found to be EPR active. However, we also found that this was a very fast reaction and 99% of the reaction was over within 30 s to yield 2,4,6-trimethyl-4′-t-butylbenzophenone (eq. 11). When a more sterically hindered ketone, 2,2′4,6,6′-pentamethylbenzophenone (**6**), was allowed to react with a 10 fold excess of **4**, a deep purple color developed rapidly and the solution was found to be EPR active. Unfortunately there was no decrease in absorption observed during the ensuing 20 h period, however, 1,6-addition product was formed during this time period. It is possible that a paramagnetic intermediate as a radical pair which is formed inside the solvent cage to produce product. However, since the t-butyl radical is stable, the free ketyl radical has more time to diffuse out of the solvent cage (Scheme 1) and mask the EPR evaluation of the rest of the reaction. Therefore, it was not possible to determine the rate constant for reaction of the t-butyl-Grignard reagent with an aromatic ketone.



(11)

Conclusion

The reaction of methyl-, phenyl-, and t-butyl-Grignard reagents with substituted benzophenones was examined in order to compare the rate constant for the

formation of the product (disappearance of the ketone) with the rate constant obtained for the disappearance of the paramagnetic intermediate by EPR spectroscopy. In order to simplify the study, pseudo-first order conditions with respect to the Grignard reagent were employed. We found that the concentration of the paramagnetic intermediate generated in the reaction was shown to decrease in a first order fashion with a pseudo-first order rate constant (k_{EPR}) which is consistent with the pseduo-first order rate constant ($k_{profile}$) describing the rate of disappearance of the ketone (appearance of product) in the cases of methyl- and phenyl-Grignard reagents. However, with t-butyl-Grignard reagent, the reaction proceeded either too fast (in the case of **5**) or too slow (in the case of **6**, due to the steric hindrance in the ketone) and the disappearance of the paramagnetic intermediate was masked by the higher concentration of escaped ketyl. Nevertheless, considering the available data, it seems that the rate constant for the reaction of Grignard reagents with aromatic ketones can be obtained by following the rate of disappearance of the paramagnetic intermediate or the rate of appearance of product (disappearance of ketone). The fact that the paramagnetic intermediate, in the case of the methyl- and phenyl-Grignard reagents, decreases during the same time period that the product is appearing is further evidence that the two events are related. All the results reported in this study strongly support our previous suggestion that the reaction of Grignard reagents with aromatic ketones proceeds via a single electron transfer pathway.

Experimental

General procedures and materials. Reagent grade anhydrous diethyl ether (Fisher) was distilled under nitrogen from a deep purple solution of sodium benzophenone ketyl. Samples of t-butyl chloride (b.p. 51°C, CaH_2), bromobenzene (b.p. 156°C, CaH_2), 2-methylbenzophenone (125–126°C at 0.3 mmHg) were purchased from Aldrich and purified by distillation. Reagent grade 2,6-dimethylbenzoic acid (Aldrich), $AlCl_3$ (Fisher), methyl bromide (Matheson) and mesitylene (Aldrich) were used as received. Samples of thionyl chloride (b.p. 76°C, $(PhO)_3P$) and carbon disulfide (b.p. 46°C, P_2O_5) were purchased from Fisher and purified by distillation. Resublimed magnesium (chips 99.95%) was purchased from Alfa.

Gas chromatographic analyses were conducted on a Varian 3700 (FID) instrument coupled to a Varian CDS III electronic integrator using a DB-1 capillary column. Quantitative GLC analyses were obtained with the use of response factors, corrected peak areas and using internal standards. Proton NMR spectra were recorded on a Brucker Ft 300 spectrometer using TMS as a standard.

Preparation of 2,4,6-trimethylbenzophenone (5). Following the literature procedure [15], **5** was obtained in 90% yield, b.p. 128°C/0.4 mmHg.

Preparation of 2,2',4,6,6'-pentamethylbenzophenone (6). Following the literature procedure [16], **6** was obtained in 19% yield, m.p. 85–86°C.

Preparation of Grignard reagents. Grignard reagent solutions were prepared as previously described [13]. The clear Grignard reagent solutions were standardized by standard magnesium analysis (EDTA titration), total base analysis, and halide analysis prior to use.

General procedure for kinetics experiments. Desired amounts of Grignard reagents and a solution of the ketone were combined under nitrogen in an EPR tube. The decrease of the EPR signal was monitored by repetitious scans from the time immediately after mixing the reagents. The concentration of radical species was

estimated by a comparison of the peak height of the first derivative EPR signal generated in the reaction with the peak height of the signal obtained from a sandard solution of 2,2,5,5-tetramethylpyrrolidine-3-carboxamide-1-oxyl radical [14].

For the EPR study of the reaction of CH_3MgBr (**1**) with 2-methylbenzophenone (**2**): 1 ml of a 1.32 *M* solution of **1** in ether was placed in a side bulb of an EPR tube containing 1 ml of a 0.132 *M* solution of **2** in ether in the bottom of the same tube. Immediately after mixing these reactants, the measurements of the EPR signal intensities were made at appropriate time intervals.

A reaction profile study with respect to time for the same reaction was performed by carrying out several sets of experiments and quenching each set at an appropriate time: To 1 ml of a 0.132 *M* solution of **2** in ether under N_2 was added 1 ml of a 1.32 *M* solution of **3** in ether at room temperature. After a certain time period, with stirring, the reaction mixture was quench with ammonia water and the resulting solution extracted with ether. The ether extracts were dried over $MgSO_4$ and after filtration, the solvent was removed at reduced pressure. The residue was then analyzed by proton NMR.

*Reaction of 2,4,6-trimethylbenzophenone (**5**) with t-butylmagnesium chloride (**4**)* To 0.7 ml of a 0.073 *M* solution of **5** in ether under N_2 was added 1 ml of a 0.496 *M* solution of **4** in ether at room temperature. After a certain time period, with stirring, the reaction mixture was quenched with ice water. The solution was then treated with 30% of hydrogen peroxide and extracted with ether. The extracts were dried over $MgSO_4$ and, after filtration, the solvent was removed at reduced pressure. The residue was then analyzed by proton NMR.

Acknowledgment

Acknowledgment is made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

References

1 E.C. Ashby, Pure and Appl. Chem., 52 (1980) 545 and ref. cited herein.
2 E.C. Ashby, J. and R. Bowers, DePriest, Tetrahedron Lett., 21 (1980) 3541.
3 E.C. Ashby, J.R. Bowers, Jr. J. Am. Chem. Soc., 103 (1981) 2242.
4 T. Holm, Acta Chem. Scand., B, 37 (1983), 567 and ref. cited herein.
5 J.F. Fauvarque, and E. Rouget, C.R. Acd. Sci. Paris, Ser. C, 267 (1968) 1355.
6 C. Blomberg, R.M. Sallinger, and H.S. Mosher, J. Org. Chem., 34 (1969) 2385.
7 T. Holm, and I. Crossland, Acta Chem. Scand., B, 25 (1971) 59.
8 M. Ōkubo, Bull. Chem. Soc. Japan, 48 (1975) 2057.
9 M. Ōkubo, Bull. Chem. Soc. Japan, 48 (1975) 1327.
10 M. Ōkubo, Bull. Chem. Soc. Japan, 48 (1975) 1057.
11 L.G. Lopp, J.D. Buhler, and E.C. Ashby, J. Am. Chem. Soc., 97 (1975) 4966.
12 E.C. Ashby, and T.L. Wiesemann, J. Am. Chem. Soc., 100 (1978) 189.
13 E.C. Ashby, J. Laemmle, and H.M. Neumann, J. Am. Chem. Soc., 94 (1972) 5421.
14 J.E. Wertz, and W.S. Bolton, Electron Spin Resonance: Elementary Theory and Practical Application, McGraw Hill, New York, 1972, p. 462.
15 P.H. Gore, and J.A. Hoskins, J. Chem. Soc. C, (1970) 517.
16 M. Weiler, Chem. Ber., 32 (1899) 1908.

Tetrahedron Letters,Vol.26,No.39,pp 4691-4694,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

Evidence for Single Electron Transfer in Metal-Halogen Exchange. The Reaction of Organolithium Compounds with Alkyl Halides.

E.C. Ashby*, Tung N. Pham and Bongjin Park

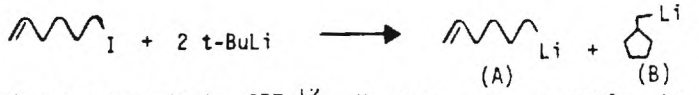
School of Chemistry, Georgia Institute of Technology, Atlanta, GA 30332

Abstract: The reaction of t-BuLi with cyclizable 1° and 2° alkyl halide radical probes at low temperature produced stable cyclized and uncyclized organolithium products as well as cyclized hydrocarbons which clearly indicate the presence of radical intermediates during the course of these reactions.

For many years, the exchange of halogen and lithium atoms in the reaction of an organic halide with an organolithium compound has been known as metal-halogen exchange (eq. 1).[1-5]

$$RLi + R'X \rightleftharpoons R'Li + RX \qquad (1)$$

Russell suggested that such reactions proceed by single electron transfer[6] (SET), although, there are several references in the literature that suggest that the reaction pathway is heterolytic in nature.[7] Among the experimental observations supporting radical intermediates in the reaction of RLi with R'X are the following: (a) formation of 2,3-dimethyl-2,3-diphenylbutane when the reaction is carried out in cumene[8]; (b) formation of the trityl radical from trityl chloride[9]; (c) nuclear polarization in the olefin products[10] or in the alkyl halide[11]; and (d) the formation of the expected coupling and disproportionation products of R and R'.[8-11] In 1984 Bailey reported that 6-iodo-1-hexene, when treated with t-BuLi at -23°C, undergoes intramolecular cyclization (eq. 2), which seemed to indicate that



(2)

metal-halogen exchange proceeds by SET.[12] However, more recently, he reported[13] that 5-hexenylithium (A) cyclizes to (B) at -23°C. Thus indicating that cyclize product (B) could have been formed from (A) after the reaction of 6-iodo-1-hexene with t-BuLi was complete. Recently Newcomb has also challenged Bailey's results and the SET nature of metal-halogen exchange. He concludes that, "the major pathway for cyclization of the 6-halo-1-hexenes is now known to be the anion route".[14] However, based on the results reported herein involving the reaction of t-BuLi with three different alkyl halide radical probes, including 6-iodo-1-hexene, we conclude that metal-halogen exchange does indeed involve the intermediate formation of radicals.

Prior to Bailey's latest report, we had found that the reaction of t-BuLi with 6-bromo- and 6-iodo-1-hexene in pentane-Et_2O at -23°, and even -78°C, produced both uncyclized (A) and

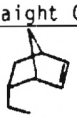
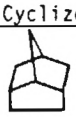
cyclized (B) organolithium product. However, the product ratio (A:B) changed on standing even at -78 °C. On the other hand, when we carried out this reaction by addition of the reagents at -130 °C, we found that the reaction was complete in 5 minutes and, the ratio of A:B (81:19) did not change over a four hour period. The cyclized product therefore does not arise from the cyclization of the hexenyllithium after it is formed.

In order to explore the mechanism of metal-halogen exchange further, we allowed two additional cyclizable alkyl halide radical probes[15] to react with t-BuLi in pentane/ether at -78°C. In the table are presented data for the reactions of endo-5-(2'-bromoethyl)-2-norbornene (1) and 6-bromo-1-heptene (5). When a 0.1 M solution of (1) was allowed to react with a 0.2 M solution of t-BuLi in pentane/ether (4:1 ratio)[16] at -78°C, followed by quenching with D_2O after 30 min. and the products analyzed by GLC, we obtained an 82% yield of (2) and a 15.3% yield of (3), which contained 61% d_1 and 60% d_1 respectively (exp 2). The ratio of (2) to (3) remained constant over a period of 24 hrs (exps. 1-3), indicating that cyclized product (3) is formed during, not after the reaction is over.[17] In an attempt to make the organolithium compound (2) more carbanionic in order to increase its chances of carbanion cyclization to product (3), we treated the reaction mixture with TMEDA, HMPA and 18-crown-6 at -78 °C after the reaction was over (exps. 4-6). We observed that organolithium compounds (2) and (3) were indeed made more carbanionic since more ether cleavage products (hydrocarbon) were formed; however, no additional cyclization was observed. The results of exp. 2 show also that 39% of (2) and 40% of (3) is straight-chain and cyclized hydrocarbons, respectively, produced before hydrolysis. The hydrocarbon formation is probably the result of a radical precursor (radical abstraction of hydrogen from solvent or RLi since carbanion cleavage is too slow at -78 °C to account for such a high degree of hydrocarbon formation after 10 min of reaction). All of the above data are consistent with the formation and cyclization of a radical intermediate.

Furthermore, when 6-bromo-1-heptene (5) was treated with t-BuLi in pentane/ether (3:2 ratio) at -78°C, 1-heptene (6) and 1,2-dimethylcyclopentane (7) were obtained (on reaction with D_2O) in 63.2% and 37% yield, respectively. The ratio of cis to trans-1,2-dimethylcyclopentane (7) was 3.9 (exp. 7). Recently, Garst et al[18] reported a cis/trans ratio of 0.32 in the reaction of 6-bromo-1-heptene with a sodium-mirror and concluded that 2-methyl-5-hexenyl sodium resembles a carbanion and cyclizes to give predominately the trans isomer, whereas the cis/trans ratio observed here (3.9) is what is to be expected and what has been observed earlier for radical cyclization.[19] The product ratio (6:7) remained constant up to 24 hrs and also was constant after adding lithium complexing agents (HMPA, TMEDA, 18-crown-6) (exps. 8- 11).

All of the above data suggest the following mechanism (Scheme I): t-BuLi transfers an electron to the alkyl halide radical probe in the first step to form a radical anion-radical cation pair. The radical anion rapidly dissociates to radical (C), which then can receive another electron from t-BuLi to give the straight-chain compound (D) which on reaction with D_2O gives (2). (C) can also abstract hydrogen from solvent to form (2) or cyclize to give radical (E). Radical (E) can then further abstract hydrogen from solvent to give (3) or react with t-BuLi to give (F).

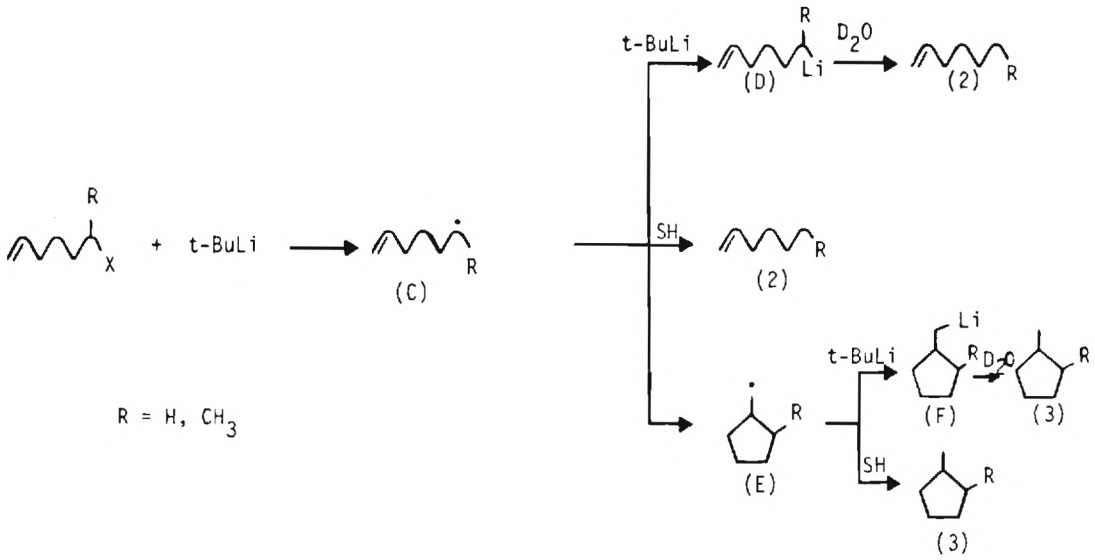
Table. Reactions of 1° and 2° Alkyl Bromides with t-BuLi at -78 °C[a]

Exps	RBr	Time	Additive	% Yield of Hydrocarbon formed on reaction with D_2O[b] Straight Chain	Cyclized	Ratio
				 (2)	 (3)	(2:3)
1		10	none	75.9 (61.8% d_1)	13.2 (55.1% d_1)	5.7
2	(1)	180	"	82.0 (60.8% d_1)	15.3 (59.9% d_1)	5.4
3		1140	"	83.0 (60.8% d_1)	15.0 (62.6% d_1)	5.5
4		240	2 TMEDA[c]	82.1 (60.8% d_1)	16.2 (52.6% d_1)	5.1
5		240	4 HMPA[c]	82.0 (56.8% d_1)	15.0 (30.7% d_1)	5.5
6		240	2(18-Crown-6)[c]	81.5 (51.9% d_1)	16.7 (32.4% d_1)	4.9
				 (6)	 (7)	(6:7)
7	 (5)	10	none	63.2	37.0(3.9)[d]	1.7
8		1140	none	62.7	35.4 (4.0)	1.8
9		240	2 TMEDA[c]	61.1	37.5 (4.1)	1.6
10		240	4 HMPA[c]	64.0	33.5 (4.1)	1.9
11		240	2(18-Crown-6)[c]	63.8	34.2 (4.0)	1.9

[a]Reactions conducted using 0.1 M initial concentration of organic halides. [b]Percent yield of hydrocarbon determined by gas chromatography using a 30 m capillary column of DB.1 at 70° - 150° for 2 and 3 and at 30°/6 min to 250° for 6 and 7 with a flame ionization detector calibrated with 1,5-cyclooctadiene and n-octane as the internal standards. [c]Additives were added at -78°C after the reaction was complete. [d] Cis/trans ratio of 1,2-dimethylcyclopentane.

Acknowledgement. We would like to acknowledge the National Science Foundation, Grant No. CHE 78-00757 for support of this work.

Scheme I



References

1. H. Gilman and A. L. Jacoby, J. Org. Chem., 3, 108 (1938).
2. G. Wittig, U. Pockels and H. Droge, Chem. Ber., 71, 1903 (1938).
3. H. Gilman and R. G. Jones, Org. Reactions, 6, 339 (1951).
4. R. G. Jones and H. Gilman, Chem. Rev., 54, 838 (1954).
5. B. J. Wakefield, "The Chemistry of Organolithium Compounds"; Pergamon Press: New York, Vol. 1, 43 (1982).
6. G. A. Russell, E. G. Janzen, and E. T. Strom, J. Am. Chem. Soc., 86, 1807 (1964).
7. G. A. Russell and D. W. Lamson, ibid, 91, 3967 (1969).
8. Bryce-Smith, J. Chem. Soc., 1603 (1956).
9. J. Schmidlin, Chem. Ber., 43 1137 (1910).
10. H. R. Ward and R. G. Lawler, J. Am. Chem. Soc., 89, 5518 (1967).
11. A. R. Lepley, Chem. Commun., 64 (1969).
12. William F. Bailey, R. P. Gagnier and J. J. Patricia J. Org. Chem., 49, 2098 (1984).
13. Private Communication, W.F. Bailey to E.C. Ashby.
14. M. Newcomb, W.G. Williams and E. L. Crumpacker, Tetrahedron Lett. 1183 (1985).
15. E. C. Ashby and Tung N. Pham, Tetrahedron Lett., 25, 4333 (1984).
16. J. F. Eastham and G. W. Gibson, J. Am. Chem. Soc., 85, 2171 (1963); C. G. Screttas and J. F. Eastham, ibid., 88, 5668 (1966).
17. The referee suggested that the cyclized product is due to the reaction of the alkenyllithium with t-butyl halide. However, when one equivalent of t-butylbromide was added to the reaction mixture from exp. 1 the ratio of products (2:3) remained constant.
18. J. F. Garst and J. B. Hines Jr., J. Am. Chem. Soc., 106, 6443 (1984).
19. E. C. Ashby, R. N. DePriest and Wei-Yang Su, Organometallics, 3, 1718 (1984).

(Received in USA 6 July 1985)

G-33-601

School of Chemistry
(404) 894-4002 (Tel.)
(404) 894-7452 (Fax)

Georgia Institute of Technology
Atlanta, Georgia 30332
A Unit of the University System of Georgia

July 18, 1990

Dr. Fillmore Freeman
National Science Foundation
1800 G Street N.W.
Washington, DC 20550

Dear Dr. Freeman,

Attached is the final report for my NSF grant CHE-840 3024. Once again I thank you and NSF for the opportunity to have done this research and to continue to extend our efforts with the aid of the new grant.

Sincerely,

E.C. Ashby

Enclosure

ams

APPENDIX VII

NATIONAL SCIENCE FOUNDATION
Washington, D.C. 20550

FINAL PROJECT REPORT
NSF FORM 98A

PLEASE READ INSTRUCTIONS ON REVERSE BEFORE COMPLETING

PART I–PROJECT IDENTIFICATION INFORMATION

1. Institution and Address	2. NSF Program	3. NSF Award Number
Georgia Institute of Technology Atlanta, GA 30332	CHE - 8403024	
	4. Award Period From 6/1/84 To 5/31/90	5. Cumulative Award Amount 580,200

6. Project Title
Single Electron Transfer. A Major Reaction Pathway in Organic Chemistry

PART II–SUMMARY OF COMPLETED PROJECT *(FOR PUBLIC USE)*

The main thrust of our work has been the gathering of evidence to support the proposition that single electron transfer is a major reaction pathway in organic chemistry. In the past five years twenty-four papers have been published, and three have been submitted for publication in the areas supported by NSF. Particularly, we have found that well known reactions that have been considered to be classic polar processes actually proceed, at least to some extend, by a SET pathway involving radical intermediates. In this connection we have studied the reactions of alkyl halides with nucleophiles ($LiAlH_4$, Me_3Sn^-, enolate anions, RS^-, NR_2^-, PR_2^-, OR^-, RMgX, RLi and $LiCuR_2$) and the reactions of ketones with the nucleophiles (alkoxides, enolate anions, OH^- and ylids). We have shown that inversion of configuration for a S_N2 Process involving alkyl iodides can be explained in terms of a SET process in which the product is formed from the radical-anion pair. Recent results also show that 1^0alkyl halides can react with certain nucleophiles to form radical, carbanion and carbene intermediates. We have demonstrated that the model system and rate constant data used to argue against the conclusions of our work is based on an invalid model system and rate constant calculations that do not take into consideration radical chain processes which are in operation. We believe that the results of the past five years definitely establish single electron transfer as a major reaction pathway in organic reactions.

PART III–TECHNICAL INFORMATION *(FOR PROGRAM MANAGEMENT USES)*

1. ITEM *(Check appropriate blocks)*	NONE	ATTACHED	PREVIOUSLY FURNISHED	TO BE FURNISHED SEPARATELY TO PROGRAM	
				Check (✓)	Approx. Date
a. Abstracts of Theses		X			
b. Publication Citations		X			
c. Data on Scientific Collaborators	X				
d. Information on Inventions	X				
e. Technical Description of Project and Results		X			
f. Other *(specify)*					

2. Principal Investigator/Project Director Name *(Typed)*	3. Principal Investigator/Project Director Signature	4. Date
Eugene C. Ashby		7/16/90

NSF Form 98A (3-83) Supersedes All Previous Editions

Form Approved OMB No. 3145-0058

Part III. Technical Information

(a) Abstracts of Theses

SINGLE ELECTRON TRANSFER IN THE REACTIONS OF AROMATIC KETONES AND ALKYL HALIDES WITH ENOLATES AND ALKOXIDES

A THESIS

Presented to

The Faculty of the Division of Graduate Studies

By

John N. Argyropoulos

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy in the School of Chemistry

Georgia Institute of Technology

June 1985

SUMMARY

A variety of methods were utilized for the detection of radical intermediates in the reactions of nucleophiles with alkyl halides and aromatic ketones. An attempt was also made to determine whether the formation of products occurred via the radical intermediates.

In the reaction of an enolate -lithiopropiophenone- with primary alkyl halides and tosylate, the method for detecting a radical intermediate involved the use of a cyclizable radical probe. For example, when 2,2-dimethyl-1-iodo-5-hexene was allowed to react with lithiopropiophenone, cyclized products were formed which were indicative of a radical precursor. Furthermore, the effects of radical scavengers, solvent, leaving group, and hydrogen-atom donors suggested that a primary neopentyl-type iodide reacts with enolates via a radical intermediate, whereas the corresponding bromide and tosylate give no indication that they react with enolates by a radical process.

The aldol condensation reactions of pre-formed enolate anions with diaryl ketones gave rise to paramagnetic intermediates as determined by EPR spectroscopy. The concentration of the radical species was found to increase when the diaryl ketone was substituted with sterically demanding groups. Furthermore, a kinetic analysis suggested that diaryl ketones react with lithium enolates to give condensation products via paramagnetic intermediates.

The Meerwein-Ponndorf-Verley reduction of benzophenone by lithium alkoxides was also observed to give a paramagnetic intermediate by EPR spectroscopy. The radical species was identified as the lithium ketyl of benzophenone, and was found to abstract a β-hydrogen from the alkoxide. The source of ketyl was found to be twofold: a one-electron transfer to benzophenone from both the alkoxide and benzophenone dianion.

SINGLE ELECTRON TRANSFER IN REACTIONS INVOLVING ALKYL HALIDES WITH NUCLEOPHILES

A THESIS

Presented to

The Faculty of the Division of Graduate Studies

By

Tung Ngoc Pham

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy in the School of Chemistry

Georgia Institute of Technology

March 1986

SUMMARY

A series of experiments designed to demonstrate the occurence of radical intermediates in an electron transfer pathway for a variety of reactions have been conducted. The experimental methods employed include product studies of reactions of compounds containing structures which can undergo a characteristic radical rearrangement, radical trapping experiments, and stereochemical studies.

A variety of methods have been utilized in order to evaluate the occurence of an electron transfer pathway for the reduction of organic halides by $LiAlH_4$ and $LiEt_3BH$. Direct spectroscopic observation of the trityl radical by EPR was made in the reduction of trityl bromide by $LiEt_3BH$. In addition, the reduction of a series of alkyl halides containing a cyclizable radical probe was examined and electron transfer was found to be the predominant pathway for reactions of various hydrides reagents with 6-iodo-1-heptene and 5,5-dimethyl-6-iodo-1-hexene, since cyclized hydrocarbons were major products in these reactions. It was found that the starting iodide cyclized rapidly to its corresponding cyclic isomer during the reaction using $LiAlH_4$ and AlH_3. Further detailed studies have shown that $LiAlH_4$ and AlH_3 are both responsible for the observed electron transfer phenomena in these reactions.

In addition, the reduction of 5-halo-1-cyclooctenes by $LiAlH_4$ and $LiEt_3BH$ were studied and it was found that ET is involved with the

corresponding alkyl iodide since cyclized hydrocarbon was major product in these reactions. On the other hand, for the corresponding tosylate or chloride, S_N2 was found to be the major pathway since only straight-chain hydrocarbon was produced. In the case of 5-bromo-1-cyclooctene, it appears that S_N2 and ET are in competition with S_N2 being strongly favored except when a very stable radical such as the trityl radical is produced.

Additional evidence indicative of radical intermediates in these reactions were obtained from reductions of the 5-iodo-1-cyclooctene with $LiAlD_4$ and $LiEt_3BD$ with the presence of the radical traps DCPH and 1,4-cyclohexadiene, which were shown to transfer a hydrogen atom to the radical intermediates. Moreover, DCPD also was used as trapping agent in the reductions of 5-iodo-1-cyclooctene by $LiAlH_4$ and $LiEt_3BH$.

New primary radical probes, (endo)-5-(2'-haloethyl)-2-norbornenes, have been synthesized and its corresponding alkyl radical has been shown to cyclize 100 times more rapidly than the corresponding 5-hexene-1-yl radical. Therefore, a variety of nucleophiles have been used to react with these radical probes in order to detect radical intermediates which were not observed previously using the 5-hexenyl radical probe.

In the reduction of alkyl iodides by $LiAlH_4$, SET was found to be the major reaction pathway. In the reaction of Me_3SnNa with the corresponding bromide was also shown to involve radical intermediates. This conclusion was based on studies involving a lowering of the cation coordinating ability of the solvent, by running the reaction in the presence of a radical trap and by the use of cyclizable probes. The

reaction of the corresponding alkyl iodide with Me_3SnNa was also to possess an ET pathway to some extent in addition to S_N2 and HME pathways. In the reaction of $LiSPr^i$ with the new primary alkyl radical probes **1** and **2**, the alkyl iodide **1** was found to react by ET pathway to some degree. However, no evidence of SET involving the corresponding alkyl bromides was observed.

Halogen-metal exchange has been studied by allowing t-Butyllithium to react with a series of alkyl halides containing a cyclizable radical probe in order to evaluate the occurence of a radical intermediate in this reaction.

It was found that radical intermediates formed via a single electron transfer pathway are involved in the reactions of t-BuLi with (endo)-5-(2'-bromoethyl)-2-norbornene in pentane:Et_2O at -78°C, since cyclized hydrocarbon was formed during the reaction. However, there was no evidence to support an electron transfer pathway in reactions of the corresponding iodide and chloride with t-BuLi in pentane:Et_2O at -78°C since only straight-chain organolithium compound was formed. However, evidence indicative of a radical intermediates was obtained from reactions of the iodo compound with t-BuLi in pentane:Et_2O at higher temperatures (-45° and -23°) and in pure pentane at -78° and -23°C in which stable cyclized hydrocarbon product were obtained.

Lithium complexing agents such as TMEDA, HMPA and 18-crown-6 were added in these reaction mixtures in order to increase the carbanionic nature of the organolithium products with the idea that if cyclized organolithium product comes from the straight-chain organolithium product

via a carbanion intermediate, then the presence of such complexing agents should increase the carbanion of the organolithium product and thereby produce more cyclized product. It was found that cyclization of the straight-chain organolithium to the corresponding cyclized organolithium in the presence of such complexing agents is relatively slow. On the other hand, the effectiveness of the complexing agents to increase carbanion character of the straight-chain organolithium compound was demonstrated by a significant lowering of the deuterium content of the straight-chain product due to ether cleavage by the straight-chain organolithium compound.

The reactions of the 6-halo-1-heptenes with t-BuLi were also examined. It was shown that 6-bromo-1-heptene reacted with t-BuLi via a SET pathway in both pentane:Et_2O and pentane at -78°C since cyclized products with a high cis/trans ratio was the major products in these reactions. On the other hand, the reaction of the corresponding iodide with t-BuLi in pentane:Et_2O at -78°C produced a high yield of cyclized product with a low cis/trans ratio (0.52). The present understanding is that such low cis/trans ratios are not supportive of a radical intermediate. The reaction of the alkyl iodide with t-BuLi in pure pentane produced the cyclized product with a cis/trans (4.7) indicative of a radical intermediate.

Lithium complexing agents were also added to these reaction mixtures, in which the product ratio also remained constant although the deuterium concentration decrease. Hence, the presence of the cyclized products in the presence of cation complexing agents is indicative of the

formation of radical intermediates both in the presence and absence of such intermediate.

A variety of nucleophiles have been used in a study of reactions with optically active alkyl halides in order to detect the occurence of an electron pathway. It is clear from the reactions of LiSPh with optically active 2-halooctanes in DMF that electron transfer is involved and the extend of electron transfer is a function of the leaving group (Br > I > Cl > OTs) as judged from the optical purities of the substitution products. In addition, the reactions of $LiSPr^i$ with optically active 2-halooctanes were studied and it was found that ET is also involved in these reactions since the substitution products produced were more highly racemized than that with LiSPh. In the reactions of LiCN with (-)-2-bromooctane and (-)-2-iodooctane, ET was indicated by the isolation of a more racemized product than in the case of the corresponding tosylate. However, S_N2 was found to be the major reaction pathway in the reaction of LiCN with the corresponding chloride.

The stereochemistry of the reactions of 2-halooctanes with $LiSPr^i$ in different solvents was also examined. By changing the viscosity of the solvent, it has been established that radical intermediates are involved in such reactions and that the extent of ET pathway follows the trend THF > DMF > HMPA. It has also been found that ET is also a function of the leaving group and follows the trend Br = I > Cl > OTs.

In addition, the reactions of 6-bromo-1-heptene and 6-iodo-1-heptene with $LiSP^i$ in THF were also examined. No evidence for occurence of electron transfer in this reaction was observed since no

cyclized product was formed. The radical trapping agent DCPH was also used in this reaction and it was found that no trapping product was formed. In addition, the reaction of $LiSPr^i$ with (-)-2-bromooctane in the presence of DCPH also did not effect the optical rotation of the substitution product. Therefore it is suggested that the reactions of the nucleophiles with optically active alkyl halides proceed by a SET pathway in which racemization occurs inside the solvent cage.

The reactions of $LiSBu^n$ with optically active 1-halo-2,2-dimethyl-1-phenyl propanes were also examined and it is concluded that electron transfer is involved as evidenced by the partial racemization of the product.

THE MECHANISM OF REACTION OF ALKYL HALIDES WITH DIPHENYLPHOSPHIDES

A Thesis
presented to
The Faculty of the Division of Graduate Studies

By

Richard Walter Ridlehuber

In Partial Fulfillment
of the Requirements for the Degree
Master of Science in the School of Chemistry

Georgia Institute of Technology
December 1988

SUMMARY

The integrity of lithium, sodium and potassium diphenylphosphide in tetrahydrofuran was investigated using 31P NMR. Results indicate that traditional methods of preparation produce aggregates and other impurities that have gone previously unnoticed. The synthesis of pure diphenylphosphides is described, thereby establishing its integrity as a startng material for the first time.

The mechanism of the reaction of pure diphenylphosphides with cyclizable radical alkyl halide probes was studied. The effects of alkali metal cation, alkylhalide leaving group and solvent have been studied. It was determined that diphenylphosphides react primarily by a polar pathway. Product formation was maximized when reaction occurs with alkyl iodides and tosylates in nonpolar aprotic solvents.

A small amount of reduced alkyl halides were also detected. We attribute these products formation to a combination of metal halogen exchange and a radical pathway.

SINGLE ELECTRON TRANSFER IN NUCLEOPHILIC REACTIONS OF SUBSTITUTED NORBORNANES

A Thesis
Presented to

The Faculty of the Division of Graduate Studies

By

Jack Lawrence Duff

In Partial Fulfillment
of the Requirement for
the Degree of
Master of Science
In the School of Chemistry

Georgia Institute of Technology
July 1989

SUMMARY

A series of 1-substituted norbornanes was used as a substrate for reaction with various nucleophiles in an effort to determine the factors affecting single electron transfer (SET) pathways in a system where other reaction pathways are excluded.

The ability of various solvents to support SET was determined by evaluation of the rate profiles. Ether was shown to be the best solvent and hexamethylphosphoramide the worst. The ratios of substitution products to reduction products obtained suggests that solvent viscosity may play an important role.

The capability of several nucleophiles to participate in electron transfer was determined. Sodium trimethyltin was found to produce relatively fast reactions with good yields of substitution products. Diphenylphosphides were also shown to be capable of inducing reaction, while isopropylthiolate was not.

The rates of reactions of 1-substituted norbornanes were found to depend solely on their reduction potentials and not necessarily their established S_N2 fugacities. The order of reactivity was found to be iodide $>$ bromide $>$ chloride $\sim$ tosylate.

Reactions of sodium trimethyltin with 1-iodo and 1-bromonorbornane were found to be slower and to yield more reduction product in the presence of DCPH. Reduction product formed in the above reaction in the absence of DCPH was shown to result from hydrogen atom abstraction from tetrahydrofuran. No evidence was found for the involvement of a hydrogen-metal exchange pathway.

INVOLVEMENT OF RADICAL INTERMEDIATES IN THE REACTION OF ALKYL HALIDES WITH CUPRATES, THE CANNIZZARO REACTION, AND THE WITTIG REACTION

A THESIS

Presented to

The Faculty of the Division of Graduate Studies

By

David Thornton Coleman III

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy in the School of Chemistry

Georgia Institute of Technology

April 1986

SUMMARY

A number of methods were utilized to explore the occurrence of radical intermediates in 1) the reaction of alkyl halides, primarily iodides, with lithium dimethylcuprate, 2) the reaction of aromatic aldehydes with NaOH or alkoxides known as the Cannizzaro Reaction, and 3) the reaction of phosphoranes with carbonyl compounds, known as the Wittig Reaction, and the reaction of phosphoranes with activated alkenes. The experimental methods employed include product studies of radical probe systems which can undergo a characteristic rearrangement if radical intermediates are involved in the reaction (such as radical addition to a double bond to form a cyclic radical), the use of radical traps and radical chain inhibitors, and direct observation of stable radical intermediates.

The reaction of lithium dimethylcuprate with the radical probe system, 5-substituted-cyclooctene, was studied very thoroughly. In the case of the iodide, considerable amounts of cyclized products were observed. These cyclized products were shown to be formed from 2-iodo-cis-bicyclo[3.3.0]octene which was produced from the starting iodide by a free radical chain process. Extensive trapping of the free radicals by good hydrogen atom donors indicates large amounts of free radicals are produced in the reaction. These free radicals are believed to be produced by single electron transfer (SET) between the the cuprate and the iodide. In the bromide case, though the reaction is quite slow, free radical cyclization still is detected, and when

dicyclohexylphosphine (DCPH) is added to the reaction, a $S_{RN}1$ chain reaction is initiated, accelerating the reaction and producing dicyclohexylmethylphosphine as a product.

Another secondary iodide probe, 6-iodo-1-heptene, was shown to react differently, reacting much faster and producing considerably more cyclized substitution products. It was shown that p-dinitrobenzene dramatically inhibits the reaction, and this suggests that a $S_{RN}1$ reaction pathway is operating which is catalyzed by free radicals produced by SET between the cuprate and the iodide.

The primary iodide probe, 5,5-dimethyl-6-iodo-1-hexene, was shown also to have a $S_{RN}1$ reaction component, but the direct substitution is more competitive and becomes the dominant reaction pathway when p-dinitrobenzene is present as an additive. Again the presence of significant amounts of free radicals was believed to be due to the occurence of SET.

Radical intermediates were detected by ESR spectroscopy in the Cannizzaro reaction of aromatic aldehydes with NaOH or potassium tert-butoxide, and these radical intermediates were identified tentatively in many cases as the radical anion of the aldehyde involved. These intermediates were shown to appear and disappear during the time frame product formation occurred in these reactions. When substituted benzaldehydes having a methyl group at the ortho position were allowed to react, significant amounts of a dimeric product believed to be formed by hydrogen atom abstraction from the ortho methyl group followed by coupling were observed.

In the reaction of various aldehydes and ketones with phosphoranes, known as the Wittig Reaction, no radical intermediates attributable to this reaction were detected by ESR. However, many of the activated alkenes formed by this reaction were shown to form radical species upon reaction with phosphoranes, either in the original reaction due to excess phosphorane or a slow initial reaction, or when isolated and allowed to react with various phosphoranes. This reaction of phosphoranes with alkenes leads to predominantly high molecular weight products when significant radical concentrations were detected by ESR.

SINGLE ELECTRON TRANSFER IN REACTIONS INVOLVING ALKYL HALIDES WITH LITHIUM ALKYLAMIDE, LITHIUM ALKYL AND LITHIUM METAL.

A THESIS

presented to

The Faculty of the Division of Graduate Studies

By

Bongjin Park

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy in the School of Chemistry

Georgia Institute of Technology

August 1988

SUMMARY

A variety of methods were utilized to explore the occurrence of radical intermediates in (1) the reaction of alkyl halides, mainly iodides, with lithium diisopropylamide (LDA), (2) the formation of organolithium compounds from the reaction of alkyl halides with Li, and (3) the reaction of alkyl halides with t-BuLi which is known as Halogen-Metal Exchange (HME). The experimental methods conducted include product studies of radical probes which can undergo a charactteristic radical cyclization if a radical intermediate is present in the reaction, the use of radical traps, radical-anion inhibitors, and carbene trapping agents. CIDNP and spin trapping techniques were also employed.

An attempt has been made to determine the mechanism of reaction of alkyl halides with LDA. A variety of methods were utilized to study the mechanism of reaction of 6-iodo-5,5-dimethyl-1-hexene and its bromo-, chloro-, and tosylate derivatives with LDA. In the reaction of 6-iodo-5,5-dimethyl-1-hexene with LDA in THF, both SET (product B) and carbene /carbenoid (products A, C, D and E) processes occurred simultaneously. However, when the bromide which has a reduction potential higher than that of the iodide, was allowed to react with LDA, the carbene/carbenoid process was predominant.

When the chloride was allowed to react with LDA, no SET product (B) was observed, but a carbene/carbenoid process had occurred (products A, C, D and E). This is the first time that a carbene intermediate has been detected in the reaction of an alkyl monohalide with any nucleophile.

The formation of organolithium compounds in the reaction of alkyl halides with lithium metal apparently proceeds via a radical intermediate. This radical intermediate was detected by PBN using a spin trapping technique. This observation provides the first spectroscopic evidence of a radical intermediate in the reaction of an alkyl halide with lithium metal. In contrast, when we studied the reaction with several primary and secondary alkyl halide cyclizable probes at various temperatures (R.T., 0^0C, -13^0C, -23^0C, -44^0C, and -78^0C), we failed to obtain evidence of a radical intermediate in the formation of alkyllithium compounds from alkyl halides and lithium. Also, CIDNP studies did not give any evidence of a radical intermediate in the reaction of alkyl halides with lithium metal.

The reaction of alkyl halides with t-BuLi was studied by using cyclizable alkyl halides as radical probes. The resulting product was hydrolyzed with D_2O in an attempt to determine the nature of the products produced. Unfortunately the straight chain alkyllithium compounds produced cyclized to the corresponding cyclic alkyllithium compound when D_2O was employed as a hydrolyzing agent. However, when we

changed hydrolyzing agent from D_2O to EtOD or EtOH, we found only one product which is the straight chain hydrocarbon having a high deuterium content (88%). Therefore, all the results obtained from hydrolysis with D_2O were found to be invalid in the study of the mechanism of HME due to the instability of the straight chain alkyllithium compound produced during the reaction. Nonetheless, we found evidence that the hydrogen atom source involved in abstraction by the radical is t-BuLi mostly through the intermediacy of t-BuX (X = I).

Part III. Technical Information

(b) Publication Citations

Publication Citations (the past five years, June 1, 1984-December 31, 1988)

Since the last proposal submitted five years ago, the following reactions have been studied in detail, the work completed and results published. The reactions fall into two major categories: I, the reactions of alkyl halides with nucleophiles and II, the reactions of aromatic ketones with nucleophiles.

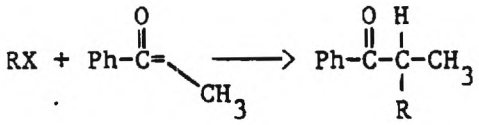
I. $RX + Y^- \longrightarrow RY + X^-$

(1) $RX + LiAlH_4 \longrightarrow RH$

J. Org. Chem. **1984**, 49, 3545
J. Org. Chem. **1984**, 49, 4505
J. Org. Chem. **1984**, 51, 3598
Tetrahedron Lett. **1987**, 28, 3183
Tetrahedron Lett. **1987**, 28, 3197
J. Org. Chem. **1988**, 53, 6156
Acc. Chem. Res. **1988**, 21, 414

(2) $RX + Me_3Sn^- \longrightarrow RSnMe_3$

Organometallics **1984**, 3, 1718
Organometallics **1984**, 4, 1493

(3) 

J. Org. Chem. **1985**, 50, 3274

(4) $RX + SR'^- \longrightarrow RSR'$

J. Org. Chem. **1985**, 50, 5184

(5) $RX + R'Li \longrightarrow RLi + R'X$

Tetrahedron Lett. **1985**, 26, 4691
J. Org. Chem. **1987**, 52, 0000

(6) $RX + LiCuR'_2 \longrightarrow R - R'$

J. Org. Chem. **1987**, 4554

(7) New Radical Probes

Tetrahedron Lett. **1984**, 25, 4333

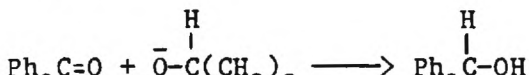
(8) $RX + OH^- \longrightarrow ROH + X^-$

Tetrahedron Lett. **1984**, 25, 5107

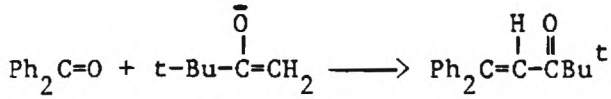
(9) $RX + Mg \longrightarrow RMgX$

J. Org. Chem. **1988**, 53, 6068

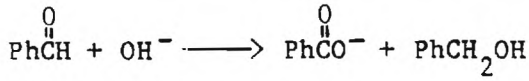
II. $Ph_2C{=}O + Y^- \longrightarrow$

(1) 

Tetrahedron Lett. **1986**, 27, 465
J. Org. Chem. **1986**, 51, 472

(2) 

Tetrahedron Lett. **1984**, 25, 7
J. Org. Chem. **1986**, 51, 3593

(3) 

J. Org. Chem **1987**, 52, 4079

Part III. Technical Information

(e) Technical Description of Project and Results

We have defined a SET reaction as one that involves the transfer of an electron from a nucleophile to a substrate to form a radical intermediate. This radical intermediate can then be involved in a stochiometric reaction (geminate coupling), or a radical chain process (e.g. $S_{RN}1$ pathway) or any other number of events to form a product. Whether or not reactions are polar in nature or involve radical intermediates on their way to form product, is a question of recent origin and is of outmost importance in the area of organic reaction mechanisms. The following report summarizes results over the past five years from our research group dedicated to determining the importance of SET in organic reaction mechanisms.

I. Reactions of Alkyl Halides with Nucleophiles

(1) Reactions of Alkyl Halides with $LiAlH_4$[1]

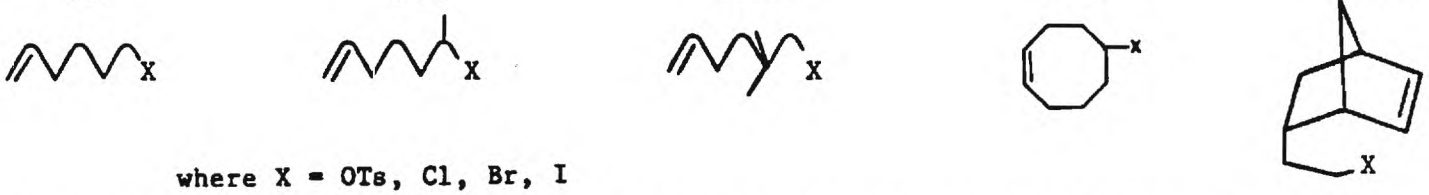
The reaction of an alkyl halide with $LiAlH_4$ is considered to be an important reaction in organic chemistry and numerous studies have been carried out to determine the mechanism of this reaction.[2] Lithium aluminum hydride has been considered to react as a nucleophile via a S_N2 process[2-7] although pathways involving radical intermediates have been proposed.[8-12] The most definitive work in this area is by Eliel[13] who showed that $LiAlD_4$ reacted with (+)-1-chloro-1-phenylethane with inversion of configuration.

Since we had found earlier that $LiAlH_4$ reacts with polynuclear hydrocarbons to form the corresponding radical anion,[14] we suspected that $LiAlH_4$ might also act as a one electron donor toward other compounds with similar reduction potentials. We studied the occurrence of SET in the reduction of trityl halides with $LiAlH_4$ (and several other metal hydrides) by a variety of methods. We observed high concentrations of the trityl radical by ESR on reduction of trityl bromide by $LiAlD_4$ and proposed a one electron transfer process to describe the pathway (eq. 1).[15]

$$Ph_3CBr + LiAlD_4 \longrightarrow Ph_3CBr^{\cdot-} \longrightarrow Ph_3C^{\cdot} \longrightarrow Ph_3CD \qquad (1)$$

We also studied the reaction of alkyl halides with $LiAlH_4$ by using a variety of radical probes (below). Although no evidence of a radical intermediate was found using

(I) (II) (III) (IV) (V)

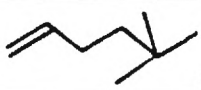


where X = OTs, Cl, Br, I

the 6-halo-1-hexenes (I), evidence for a radical intermediate was observed in all the

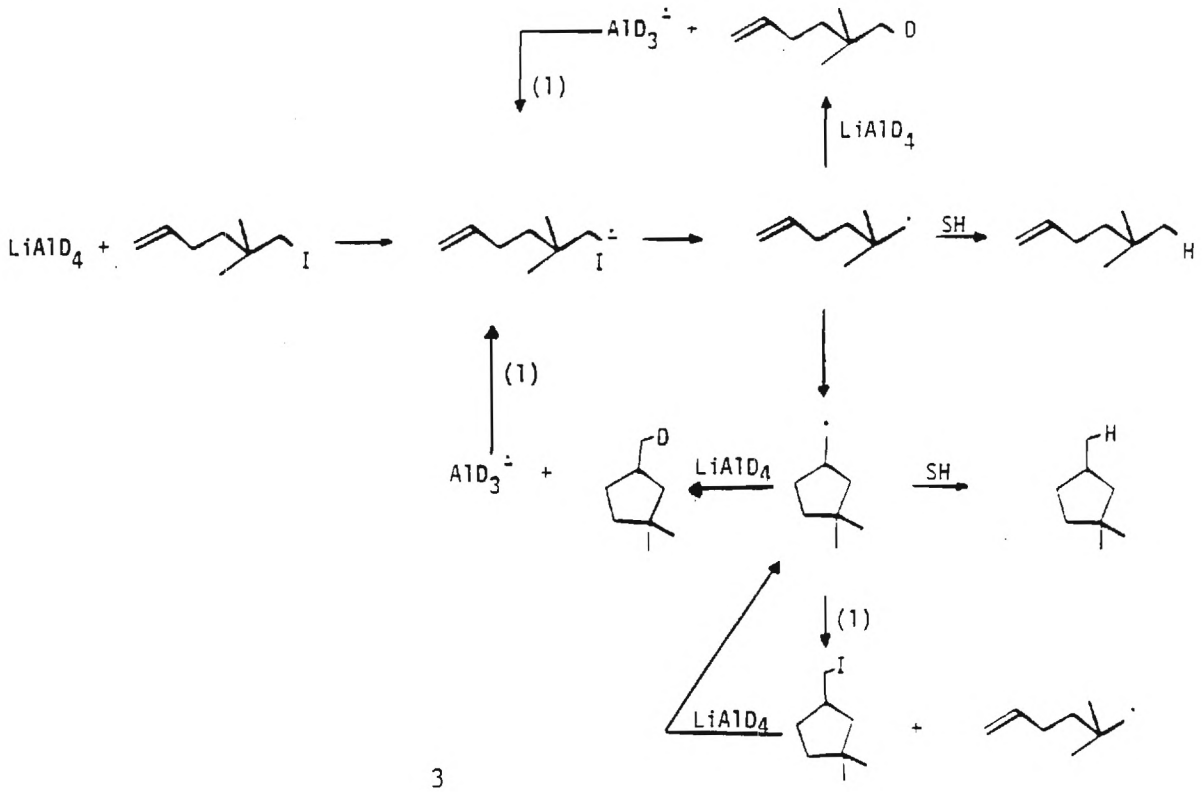
other cases (II-V) where X = I. A summary of a great deal of data is presented (Table 1)

Table 1. Reduction of 5,5-Dimethyl-6-halo-1-hexenes by $LiAlH_4$ in THF at RT for 48 Hours

RX	 ($\%d_1$)	 ($\%d_1$)
ROTs	1.8	0
RCl	0	0
RBr	9.8	7.5
RI	2.5	96
RI ($LiAlD_4$)	5.5 (69% d_1)	89 (59% d_1)

in order to establish the intermediacy of radicals in the reaction of $LiAlH_4$ with radical probe (III) although the other probes gave similar results. Compound III was chosen because S_N1 and S_N2 pathways are discouraged, therefore SET, if present, can be more easily observed. It is clearly indicated by the extent of formation of cyclized hydrocarbons that the extent of radical intermediacy is proportional to the ease of reduction of the substrate RI > RBr > RCl > ROTs. The following mechanism (Scheme 1) was proposed in 1984 and more recently modified after information was obtained to establish a

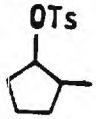
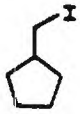
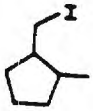
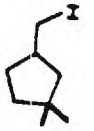
Scheme 1. Mechanism of Reaction of 5,5-dimethyl-6-iodo-1-hexene (1) with $LiAlD_4$.



radical chain process involving (3), (6) and AlH_4^-. In this way $AlH_3^{\cdot-}$ is formed which acts as a superior one electron donor toward the alkyl halide in a radical chain process. Thus a small amount of electron transfer from nucleophile to substrate can account for the large amount of product produced via a radical intermediate.

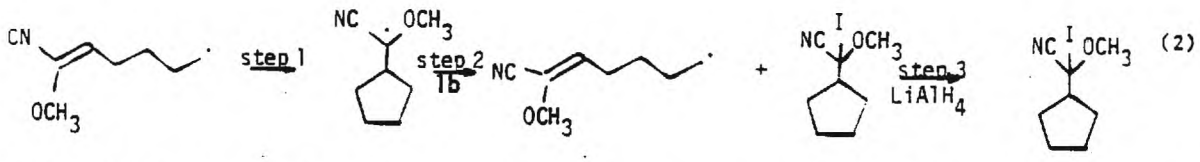
Recently, Curran[16] and Newcomb[17] have claimed that observation of cyclized products (**7, 8**) in the above reaction is not indicative of the process described in Scheme 1 (as proposed in 1984) in which intermediate (**6**) proceeds to (**7**) and (**8**), but rather a polar reaction of the cyclized iodide (**9**) with $LiAlH_4$. It appeared to us that we had already discussed this problem and answered it in previous studies.[1,18,19] In 1984, we proposed the mechanism above supported with extensive data from a variety of experiments. We monitored the appearance of cyclized halide (**9**) which we proposed was formed by a radical chain process during the reaction. We further showed that although some of the cyclized product (**7, 8**) was formed by reduction of the cyclized halide (**9**) with $LiAlH_4$, it was also clear that some of the cyclized product (**7, 8**) was formed by the reaction of the radical intermediate (**6**) with a hydrogen source other than $LiAlH_4$. Our major reason for this conclusion was based on the fact that 31% of the straight chain product (**4, 5**) and 41% of the cyclized product (**7, 8**) has a radical precursor which is abstracting hydrogen from a source other than $LiAlD_4$. We have also obtained similar results using the radical probes I-III. Furthermore the data in Table 2 show that even the cyclized iodide, when formed, is reduced, at least to some extent, via a radical intermediate. Reactions were carried

Table 2. Reduction of Alkyl Iodides with $LiAlD_4$ in THF

Exp.	RX	Metal Hydride	Cyclized Hydrocarbon
1		$LiAlD_4$	100 (100% d_1)
2		$LiAlD_4$ AlD_3	98 (90% d_1) 100 (77% d_1)
3		$LiAlD_4$ AlD_3	99 (95% d_1) 98 (74% d_1)
4		$LiAlD_4$ AlD_3	99 (98% d_1) 98 (68% d_1)

out with AlD_3 as well as $LiAlD_4$ since AlD_3 is produced as a by-product in the reaction of $LiAlD_4$ with an alkyl halide. Newcomb's assertion[17] that the initial electron transfer is due to adventitious impurities in the reaction was made with the knowledge of our 1984 report that the halide substrate was distilled and found to contain no other components as determined by glc and the $LiAlH_4$ was doubly recrystallized from distilled THF-benzene (no transition metal impurities in the $LiAlH_4$ were detected by atomic absorption analysis) and all solvents were distilled over $NaAlH_4$. Furthermore, doping experiments of the $LiAlH_4$ with $FeCl_3$, gave the same results as with pure $LiAlH_4$. There has been no evidence presented by anyone to indicate that initial electron transfer is due to adventitous impurities in the reactants.

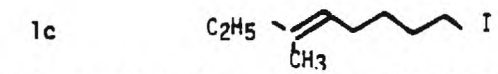
More recently[20] Newcomb reported evidence to support his contention that cyclized product (7,8) is a result solely of reduction of 9 by $LiAlH_4$. The proposal was a reasonable one based on the idea that if a model system is used that will result in rapid cyclization (eq.2,step 1), but not result in the formation of cyclized product (step 3), it



(2)

is because step 2 does not take place. Step 2 in this system would not be expected to occur since it results in the formation of a less stable radical. The conclusion was then that all cyclized product comes via steps 2 and 3 since no cyclized product was formed in this case.

We were able to show [21] that the model system used by Newcomb (1b) is an invalid probe based on the fact that the Z/E ratio of the reactant (38/62) substantially changed in the product (16/84) indicating that the double bond was involved in the reaction (possibly by the α,β-unsaturated nitrile forming a radical anion which would prevent cyclization). We were, in fact, able to get evidence of a radical intermediate by carring out the reaction of 1b with $LiAlD_4$ in the presence of a hydrogen atom trap, cyclohexadiene. The product showed protium incorporation (5-8%) indicative of a radical precusor. Even more importantly we were able to show that a model system (1c) that mimics 1b, but that shows



no evidence of isomization of the double bond (Z/E = 41/59 in reactant and product) does indeed form cyclized product (9.6% with $LiAlH_4$ and 18.4% with $LiAlD_4$). Therefore even

though step 2 (eq.2) would not be favorable using **1c**, still cyclized product is produced indicating that step 2 is not the only pathway to cyclized product.

Stereochemical data involving the reactions of optically active 2-substituted-2-deuteriooctanes show inversion of configuration when the substituent X=OTs, Cl, and Br, but substantial racemization when X=I[22]. Since radical formation is so extensive when X=I, it is somewhat surprising that complete racemization was not observed. This can be explained by assuming that the loose radical-anion pair $[Y^{\bullet}R^{\bullet}\text{----}X^{-}]sc$, can react by racemization plus inversion (eq. 3). This matter will be discussed in more detail later in this proposal.

$$RX + Y^{-} \longrightarrow [Y^{\bullet}RX^{\ddagger -}]_{sc} \longrightarrow [Y^{\bullet}R^{\bullet}X^{-}]_{sc} \longrightarrow [Y^{\bullet}R^{\bullet}\text{----}X^{-}]_{sc} \longrightarrow RY + X^{-} \qquad (3)$$

sc = solvent cage

(2) Reactions of Alkyl Halides with Me_3Sn^- [23,24]

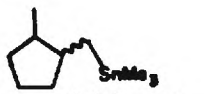
Several mechanisms have been proposed for the formation of tetraalkyltin compounds by the reaction of alkyl halides with alkali metal triorganotin compounds.[25] These proposals were based on a variety of stereochemical studies[26-28] and trapping experiments.[29,30] The three proposed pathways are described in eq. 4. Recently Kuivila has determined the

$$RX + R'_3Sn^- \longrightarrow \begin{cases} [R'_3Sn^{\delta-}\text{----}R\text{---}X^{\delta-}] \\ R'_3Sn + R^{\bullet} + X^- \\ R^- + R'_3SnX \end{cases} \longrightarrow R'_3SnR + X^- \qquad (4)$$

extent of reaction by S_N2, SET and HME (halogen-metal exchange) for a variety of reactions involving alkyl halides and sodium or lithium triorganotin compounds.[31,32] He found that reactions involving primary alkyl halides proceed exclusively by a S_N2 pathway, sterically hindered primary alkyl halides react to some extent by SET and secondary alkyl halides react by both S_N2 and SET. However, San Filippo reported that a secondary alkyl halide, (-)-2-bromooctane, reacted with $NaSnMe_3$ with predominant inversion of configuration and therefore questioned the SET nature of the reaction.[33]

We thought that this dichotomy could be resolved by the use of radical probes. Although it was reported that 6-bromo-1-hexene did not produce cyclized product when allowed to react with Me_3Sn^-, we found that 6-bromo-1-heptene did, and therefore proceeded to study this reaction in detail. The results summarized in Table 3 show that the amount of cyclized

Table 3. Reaction of 6-Halo-1-heptenes with Sodium Trimethyltin in THF at 0°C.

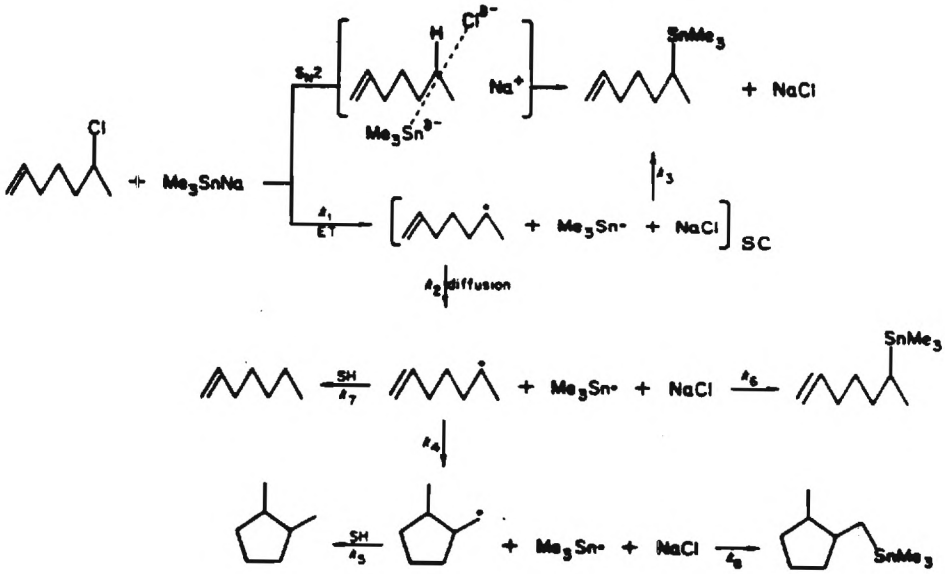
Exp		Special Conditions		 (cis/trans)		
1	OTs		96.0	0.0		
2	Cl		78.2	12.2 (4.4)		
3	Br		6.1	80.7 (3.9)		
4	I		9.5	69.2 (4.0)		
		Additive				
5	Br	DCPH	2.6	14.2 (4.2)	50.2	15.8 (4.8)
6	Br	t-BuNH$_2$	3.6	74.5 (4.0)	3.0	3.0
		Temp.°C				
7	Br	-23	16.0	76.3 (5.0)		
8	Br	-50	66.1	33.9 (6.8)		
9	Br	-78	94.8	5.2		
		Conc. (M)				
10	Br	1.0	17.9	76.9 (3.9)		
11	Br	0.2	6.7	88.2 (3.9)		
12	Br	0.043	4.7	89.2 (4.2)		
		Reaction Time (min)			**Ratio St. Chain/Cyc. Product**	
13	Br	5	3.6		4.1	
14	Br	15	5.1	24.5 (4.7)	4.8	
15	Br	60	7.4	34.5 (5.0)	4.7	
16	Br	120	12.1	48.1 (4.7)	4.0	
17	Br	300	14.2	67.7 (5.0)		

product formed is proportional to the reduction potential of RX (exps 1-4), that the cyclized product has a radical and not a carbanion precursor (exps 5-6), that viscosity at lower temperatures prevents escape of the radical intermediates from the solvent cage and thus results in the formation of less cyclized product (exps 7-9), that dilution of the reaction mixture causes an increase in the amount of cyclized product formed since cyclization is a unimolecular process (exps 10-12), and that the cis/trans ratio of the cyclized product is indicative of a radical cyclization and the ratio of straight chain to cyclized product is constant throughout the reaction (exps 13-17). The constancy of the ratio of straight chain to cyclized product shows that cyclization of the probe to the cyclized halide does not take place in this reaction, nor should it, since halogen

exchange ($6 \xrightarrow{(1)} 9$, scheme 1), although rapid for iodides, is very slow for bromides and does not take place at all for chlorides. Although Newcomb[17] and Curran[16] have recently suggested that the use of cyclizable probes to detect SET has a major flaw in that the probe cyclizes prior to reaction with the nucleophile, it is clear in this case that cyclized product is not due to halogen exchange since considerable cyclized product is formed even with the alkyl bromides and chlorides.

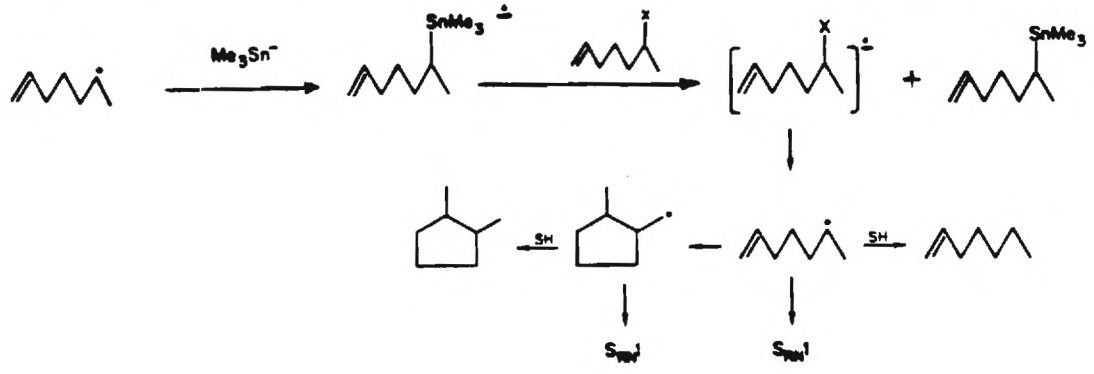
All of the studies carried out, where X=Cl, Br, and I, indicate the mechanism below shown for the chloride (Scheme 2).

Scheme 2. Mechanism of Reaction 6-Halo-1-heptenes With Me_3Sn^-



The reaction was shown to have a $S_{RN}1$ component as determined by studies using p-dinitrobenzene and di-t-butylnitroxyl radical (Scheme 3).

Scheme 3 The $S_{RN}1$ Component of the Reaction of 6-halo-1-heptenes with Me_3Sn^-



A most unusual and important result of these studies was the demonstration that the reaction of 6-bromo-1-heptene with Me_3Sn^- resulted in the formation of 80% cyclized substitution product (see Table 3) yet our own stereochemical studies involving optically active 2-halooctanes did not show extensive racemization of the product. We found that the % inversion of configuration was proportional to the reduction potential of the halide (ROTs = 100% inversion, RCl = 89%, RBr = 77%, RI = 83%), however, for such a large amount of cyclization, one would have expected much more racemization of the product. We suggest a mechanism similar to what was suggested for the reaction of 2-halooctanes with $LiAlH_4$ (eq.3).

The reaction of a series of primary alkyl bromides with Me_3SnNa was also examined. The results reported at the time were inconsistent with previous reports[34,35] that radicals are not involved.[35,36] However, by studying the effect of lowering the viscosity of the solvent, lowering the cation coordinating ability of the solvent, or running the reactions in the presence of a radical trap, it was established that radical intermediates are involved in this type of reaction at least for the systems studied. In addition, the reaction of a primary alkyl iodide containing a cyclizable radical probe with Me_3SnNa was also examined. It was found that this reaction does not react exclusively via S_N2 and HME pathways as previously reported, but also reacts via a SET pathway to a significant extent. All of the data collected in this study are completely consistent with the mechanism proposed in Scheme 2.

(3) Reactions of Alkyl Halides with Enolate Anions[38]

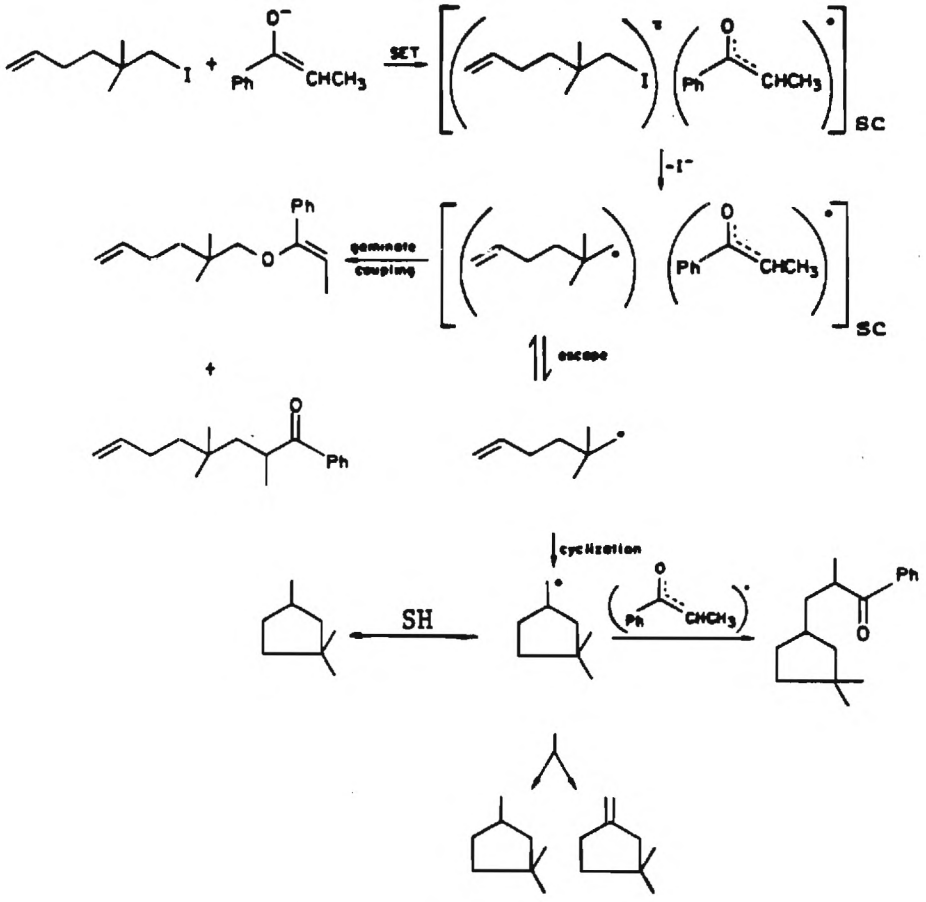
The reaction of an enolate anion with an alkyl substrate (halide or tosylate) is well recognized as an important synthetic reaction in organic chemistry.[39] Although the mechanism of this reaction is generally believed to proceed by a S_N2 process, Kornblum has demonstrated that for reactions involving p-nitrobenzyl chloride, a $S_{RN}1$ type radical-radical anion chain mechanism is involved.[40] The ability of an enolate anion to serve as a one electron donor toward a variety of other organic substrates is well documented. Examples of such substrates include p-dinitrobenzene,[41] p-nitrobenzoyl esters,[42] and diaryl ketones.[41,43] With this background, we chose to embark on a detailed mechanistic study involving lithiopropiophenone with cyclizable alkyl halide and tosylate probes.

Single electron transfer in the reaction of a model system consisting of lithiopropiophenone with primary neopentyl type alkyl halides and tosylates was investigated by (1) the use of an appropriate cyclizable alkyl halide radical probe, (2) observation of the effect of varying the leaving group on reaction rate and product

distribution, (3) studying the effect of light, di-tert-butylnitroxyl radical, and p-dinitrobenzene on the rate of reaction, (4) observing the consequence of varying solvent composition on both the reaction rate and product distribution, and (5) studying the effects of the radical traps, dicyclohexylphosphine and 1,4-cyclohexadiene, on product composition.

The radical probe chosen for the study was 5,5-dimethyl-6-iodo-1-hexene and its bromo and tosylate derivatives. All of the data collected in the various studies were consistent with the proposed mechanism (Scheme 4).

Scheme 4. Mechanism of Reaction of 5,5-Dimethyl-6-iodo-1-hexene With the Enolate of Propiophenone



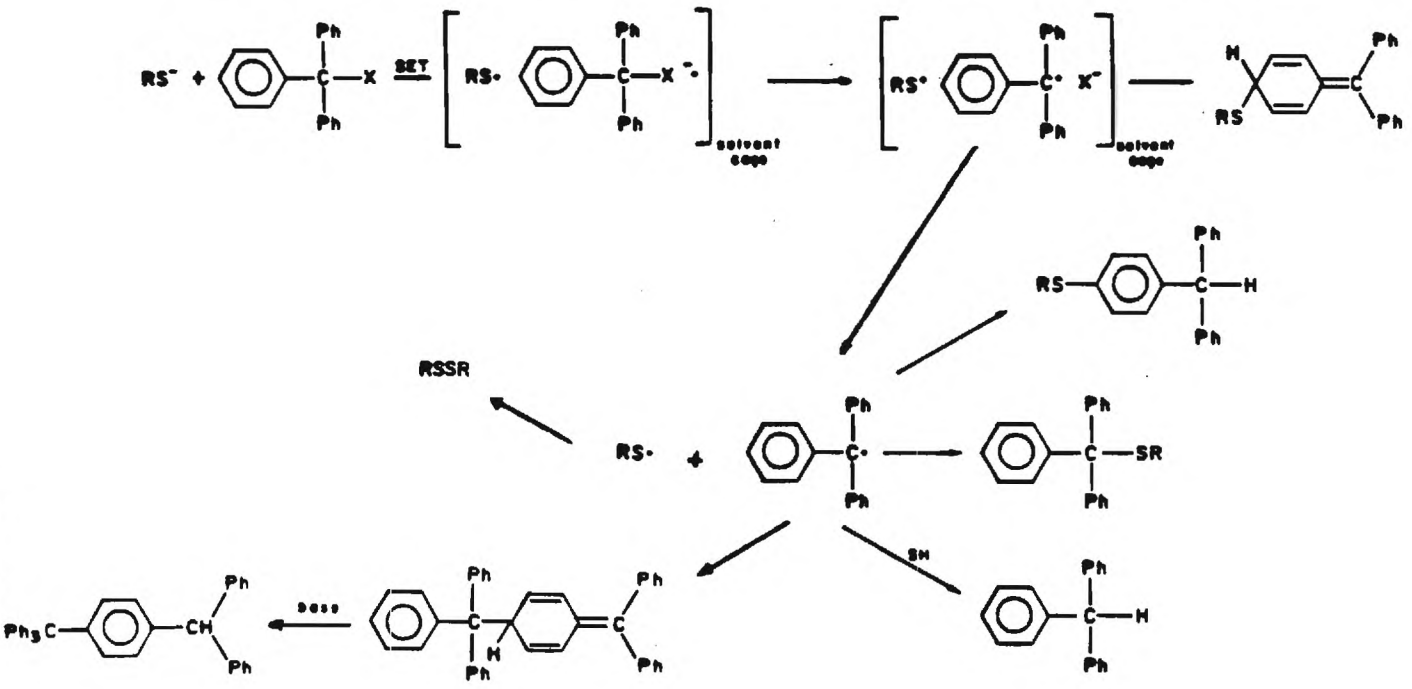
(4) Reactions of Alkyl Halides with RS^- [44]

The reaction of alkyl halides with such a good nucleophile as RS^- was thought for a long time to proceed by a S_N2 pathway.[45] Significant contributions related to the SET involvement in this reaction have been made by Russell,[46] Kornblum,[47] Bunnett,[48], Pross[49] and others. In our studies a variety of organic substrates possessing low reduction

potentials and producing stable radical intermediates were utilized in order to evaluate the one-electron transfer ability of lithium thiolates. In this connection, direct spectroscopic detection of radical intermediates was observed for the reaction of lithium thiolates with diaryl ketones, polynuclear hydrocarbons, trityl halides, and 9-bromofluorene.

A mechanistic study concerning the reaction of lithium thiolates with trityl halides was conducted in more detail by (1) carrying out a complete identification of products, (2) studying the effect of the radical trap, DCPH, on product distribution, and (3) studying the effect of light and the presence of p-DNB on the reaction rate. Thus, reactions of lithium alkanethiolates with trityl halides produced α-substitution product (Ph_3CSR), and para substitution product ($p\text{-}RSC_6H_4CHPh_2$), as well as radical by-products such as reduction product (Ph_3CH), product from dimerization of trityl radicals ($p\text{-}Ph_3CC_6H_4CHPh_2$), and product from dimerization of thiyl radicals (RSSR), all of which suggest the occurrence of SET as the predominant pathway. The reaction of lithium 2-propanethiolate with trityl bromide in THF in the presence of light or absence of light or the presence of p-DNB did not affect the rate of reaction, thus suggesting the unlikelihood of a radical-radical anion chain process. A mechanism consistent with all of the data is given in Scheme 5.

Scheme 5. Proposed Mechanism for the Reaction of Thiolates with Trityl Halides



(5) Reaction of Alkyl Halides with RLi[50]

Although metal-halogen exchange (eq. 5) is an important reaction for the preparation

$$RLi + R'X \rightleftharpoons R'Li + RX \qquad (5)$$

of organolithium compounds, the mechanism of this reaction is still controversial. We have studied metal-halogen exchange by allowing t-butyllithium to react with a series of alkyl halides containing a cyclizable radical probe in order to evaluate the occurrence of a radical intermediate in the reaction. It was found that a radical intermediate is involved in the reaction of t-BuLi with the radical probe, (endo)-5-(2'-bromoethyl)-2-norbornene in pentane:Et_2O at -78°C, since cyclized hydrocarbons were formed during the reaction. However, there was no evidence to support an electron transfer pathway in reactions of the corresponding iodide and chloride with t-BuLi under the same conditions since only the straight-chain organolithium compound was formed. On the other hand, evidence indicative of a radical intermediate was obtained from reactions of the iodo compound with t-BuLi in pentane:Et_2O at higher temperatures (-45° and -23°) and in pure pentane at -78°C and -23°C in which stable cyclized hydrocarbon product was obtained. The effectiveness of the complexing agents, HMPA, TMEDA and 18-crown-6 to increase carbanion character of the straight-chain organolithium compound was demonstrated, yet these complexing agents did not cause cyclization of the straight chain RLi compound to the corresponding cyclized compound. Reactions of the 6-halo-1-heptenes with t-BuLi were also examined. It was shown that 6-bromo-1-heptene reacted with t-BuLi via a SET pathway in both pentane:Et_2O and pentane at -78°C since cyclized product with a high cis/trans ratio was the major product in these reactions.

(6) Reactions of Alkyl Halides with $LiCuMe_2$[51]

We have completed an extensive study concerning the mechanism of reaction of alkyl halides with $LiCuMe_2$. A variety of methods were utilized to explore the occurrence of radical intermediates and free radical chain processes initiated by electron transfer in this reaction. The effect of leaving group, nature of the cuprate species, ratio of cuprate to substrate, solvent, hydrogen atom donor and other additives on the rate of reaction and product distributuion were investigated using a cyclooctenyl radical probe. The presence of radicals strongly supports SET as a major pathway for the reaction of secondary iodides with $LiCuMe_2$. There is some evidence of SET also occurring with secondary bromides; however, tosylates appear to be reacting entirely by a S_N2-like pathway. The product distribution, rate, and effect of p-dinitrobenzene on the reaction of 5-iodo-1-cyclooctene were compared with three other iodide probes and the results demonstrate that at least three reaction pathways are involved to varying degrees.

(7) New Radical Probes[52]

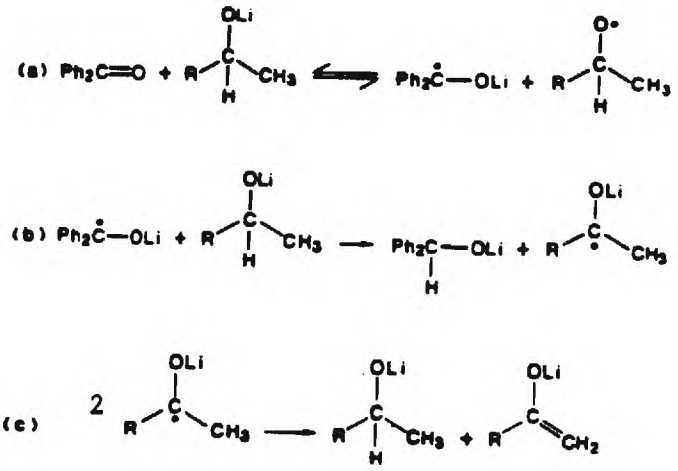
A new type of radical probe, the endo-5-(2'-haloethyl)-2-norbornenes, was prepared where the halogen = I and Br. This probe was found to cyclize over one hundred times faster than the well known 6-halo-1-hexenes (eq. 6) and has already been used to great advantage in several of our studies.

(6)

II. Reactions of Aldehydes and Ketones with Nucleophiles

Because of the page limitation for this proposal, it will be necessary to provide only a very brief summary of the reactions of aldehydes and ketones with nucleophiles. The methodology consists of following the rate of disappearance of the paramagnetic intermediate and the rate of formation of the product. If the rate constants are within experimental error of each other and if radical-anion trapping experiments are supportive, a SET mechanism is indicated. Figures (1-4), showing the rates of the individual steps, are provided for the reaction of benzophenone with lithium isopropoxide (Meerwein-Ponndorf-Verley Rx.).[53] Very similar methodology was applied in the study of the reactions of ketones with enolates (aldol Condensation),[54] the reactions of substituted benzaldehydes with OH^- or $^-OBu^t$ (Cannizzaro Rx[55]) and the reactions of ketones with ylids.[56] The figures, especially figure 4 which shows that the ketyl reacts with $^-OPr^i$ with the same rate constant as the ketone, provide strong evidence that the reaction is proceeding by the following pathway (Scheme 6).

Scheme 6. Mechanism of Meerwein-Ponndorf-Verley Reduction of Aromatic Ketones



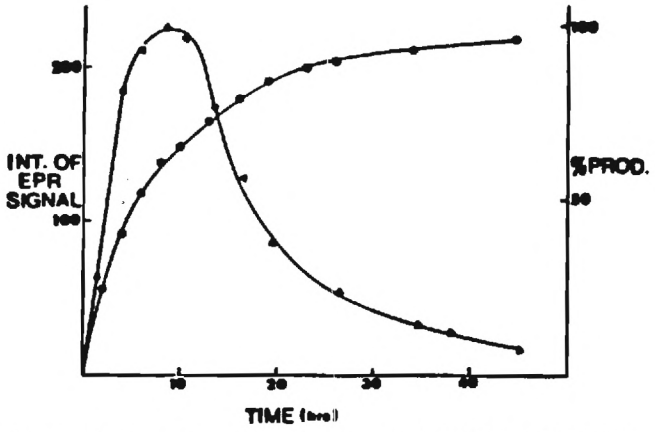


Figure 1. Reaction of benzophenone (0.076 M) with lithium isopropoxide in THF: (▲) intensity of EPR signal (mm) vs. time (h), where 1 mm = 0.01% radical; (●) reduction product (%) vs. time (h).

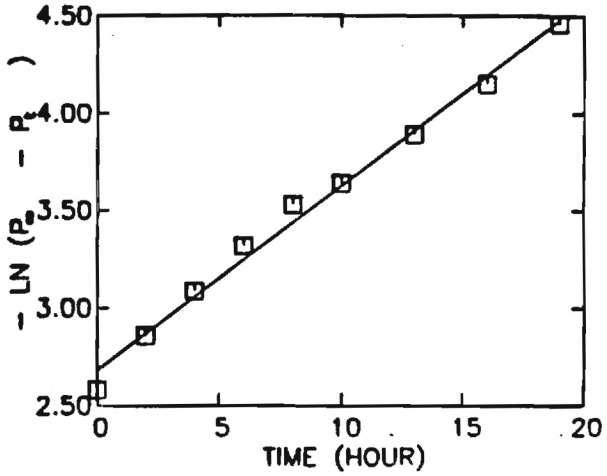


Figure 3. Plot of ln ($P_\infty - P_t$) vs. time for the pseudo-first-order formation of benzhydrol in the reaction of benzophenone with lithium isopropoxide.

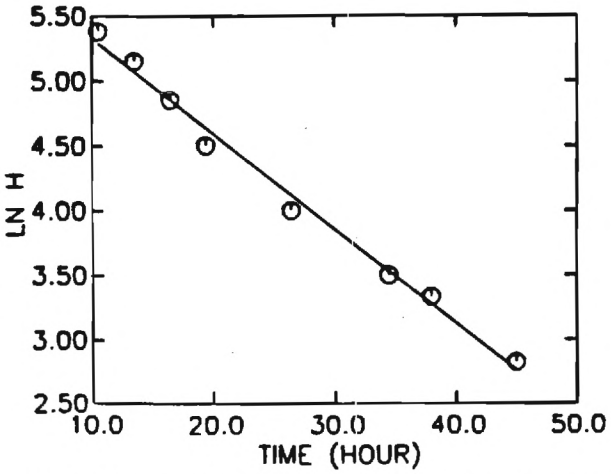


Figure 2. Plot of ln H vs. time for the first-order decay of radical intermediate in the reaction of benzophenone with lithium isopropoxide.

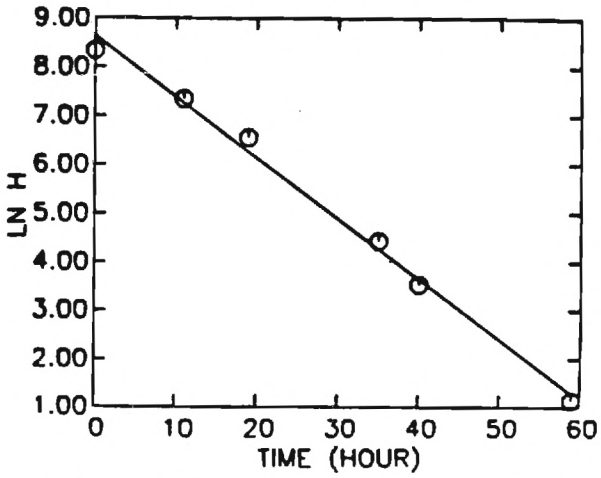


Figure 4. Plot of ln H vs. time for the first-order decay of benzophenone ketyl in the reaction of the ketyl with lithium isopropoxide.